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Testosterone Therapy of Male Eunuchoids

III. Sublingual Administration of Testosterone Compounds

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As STATED in the first paper of this series (1) entitled, 'Implantation of testosterone compounds in cases of male eunuchoidism', "the effectiveness of an endocrine preparation is measured best by its capacity to restore normal function in a characteristic endocrinopathy caused by its deficiency. Eunuchoidism, or male hypogonadism, is the clinical state in which the primary deficiency resides in the testes, and therefore it represents an ideal clinical condition for testing the effectiveness of an androgenic substance."

The clinical efficacy of parenteral administration of testosterone propionate in the treatment of male eunuchoidism and of adult forms of male hypogonadism has been confirmed abundantly. For the past 4 or 5 years this testosterone preparation in oil has been available commercially. The effectiveness of implanting pellets of crystalline testosterone compounds, principally methyl testosterone, has been reported (1). It was demonstrated that in some respects the continuous absorption from such pellets was more efficient and presumably more economical than the injection of the hormone in oil, since only approximately one-fifth of the dose was required to obtain similar results. Furthermore, the improvement achieved by such implants was maintained for about 7 weeks, while 2 to 7 injections per week were required to accomplish the same results by the parenteral method.

In the second paper of this series (2) entitled, 'Clinical comparison of parenteral, implantation, and oral administration of testosterone compounds in male eunuchoidism,' the effects produced in 3 cases by single massive implants of 600 to 800 mg. were reported. Formerly 16 to 23 tiny pellets had been introduced through a large-bore needle in doses aggregating from 83 to 195 mg. In the modified procedure a 1-inch incision was necessary and pellets of 200 mg. each were implanted. Contrary to expectations, the active stimulation was not prolonged in direct ratio to the size of the dose. The pellets ceased to be effective much sooner than was anticipated. In 2 of the 3 cases, one-fourth to one-half of the original implant was recovered subsequently. It had evidently been rendered non-absorbable by formation of a connective tissue capsule. Large implants, therefore, were disappointing with regard to both duration of effect and wastage of material. Furthermore, massive implants necessitated a minor surgical operation which did not seem warranted by the additional benefits received.

Methyl testosterone by mouth was surprisingly effective in maintaining the improved status previously attained by the parenteral or implantation methods. Indeed, the response was augmented both subjectively and objectively. The dose required in 6

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cases was 2 to 4 times the intramuscular dose. This mode of therapy was found to be the simplest, most convenient and possibly the most economical. In cases of severe eunuchoidism in adults, the initial oral dose required was between 50 and 100 mg. daily. Maintenance doses as a rule were between 10 and 30 mg. daily. Oral therapy alone produced gain in weight, elevation of the basal metabolic rate, growth of the external genitalia and prostate, more vigorous growth of sexual hair, deepening of the voice, increased libido and frequency of erections, as well as increased strength, endurance and mental and emotional animation.

In a subsequent paper (3) the clinical indications for testosterone and the various modes of administration were reviewed. Preliminary mention was made of the sublingual absorption of testosterone compounds. The purpose of the present paper is to report our clinical experiences with this method in 9 cases.

Anderson, Haymaker and Henderson (4) in 1940 reported that desoxycorticosterone dissolved in propylene glycol was equally effective, dose for dose, when it was absorbed from under the tongue as when it was administered parenterally. This discovery obviated the necessity for daily injections in patients suffering from Addison's disease (desoxycorticosterone is ineffective when swallowed). Admittedly, the same advantage does not apply to testosterone because of the remarkable oral potency of methyl testosterone. Nevertheless, we are able to report that the methyl and propionic esters of testosterone and above all pure testosterone are successfully absorbed sublingually.[1]

The solution of each of these three substances contained 25 mg. of hormone per cc. The dropper used for its administration was calibrated in 0.1 cc. divisions. The maximum amount that could be taken comfortably at one time was 0.2 cc. (which contains 5 mg. of hormone). The patient was instructed to measure the dose in the dropper, to tilt back the head and to place the measured dose under the tongue. He was instructed to hold this position, with the mouth open, until the substance was apparently absorbed, for which 2 to 5 minutes usually were required. During this time he was asked not to swallow. This procedure was repeated 2 to 5 times daily, depending on the dose required, namely 10 to 25 mg. We believe that patients probably would object to going through this performance more than 5 times a day.

While the case records for this paper were being compiled, Joel of Basle University (5), in 1942, reported that he administered testosterone sublingually in "especially hard-pressed tablets" which he considered a more convenient and pleasant-tasting vehicle than the propylene glycol solution. Each tablet contained 5 mg. of methyl testosterone. He treated 19 females, 15 of whom were suffering from climacteric disorders, 2 from dysmenorrhea and 2 from mastodynia. The dose varied from 1 tablet daily in mild cases (5 mg.) to 6 tablets daily in severe cases. The results were gratifying in most instances. Furthermore, Salmon and Geist (6) as well as Hall (7) have shown that sublingual administration of α-estradiol in propylene glycol produces a typical cornification in the vaginal smear.

Our observations with respect to sublingual administration of testosterone are confined to the male. Five of the 9 cases included in this series have been reported in previous papers (1, 2) in more elaborate detail. The patients in these 5 cases were characteristic examples of severe eunuchoidism which originated prior to normal adolescence and were exceedingly immature at the ages of 21, 24, 24, 24 and 31 years, respectively. Subsequently they had been treated either with testosterone propionate administered parenterally or with methyl testosterone administered in pellet form by implantation or in tablet form orally. They all had been vastly improved and successfully maintained by means of one or more of these procedures. Since they had been observed for a sufficiently long period of time to permit critical comparative apparaisal of parenteral, implantation and oral administration of testosterone compounds, we considered them as excellent controls for a trial of the sublingual method of administration. The remaining 4 patients in this series represent several types of male hypogonadism. None of them had received any form of testosterone therapy before. All of them displayed improvement after sublingual therapy. No other treatment was given. We therefore believe that the benefits achieved may be ascribed to the sublingual administration of testosterone.

CASE REPORTS

Case 1; R.C., (U 57397). *Case 7* in (1); *Case 1* in (2) with photographs. The patient was 24 years old when he was first seen in April, 1940, with characteristic preadolescent eunuchoidism. His height was 66.75 in. and his weight, 120 lb. He had typical disproportionately long extremities, shaved infrequently and had a high-pitched voice. The pubic hair was scant and axillary growth was moderate. The penis was small (length 5 cm.) and the testes were the size of small olive pits. The left testis was undescended. The prostate was barely palpable. The bone age was 16 to 17 (at 24 years of age).

Implants of methyl testosterone were begun on April 17, 1940. During the following 8 months 4 implants of tiny pellets were introduced subcutaneously through a large-bore needle; the dose varied from 143 to 180 mg. Marked subjective and objective improvement resulted.

[1] These preparations were supplied by The Schering Corporation, Bloomfield, N. J.

Priapism persisted for one week following the first implant. The stimulating effects lasted from 4.5 to 7 weeks after each implantation during which time the patient had frequent erections and some nocturnal emissions; he masturbated occasionally. The length of the penis had increased to 8 cm.; its circumference was 8 cm. Scrotum and testes had increased in size; the left testis had descended shortly after the first implant. The patient had gained 13 lb. and felt stronger. His voice had deepened, the body hair had increased and he shaved every week.

In December, 1940, 4 pellets of methyl testosterone totalling 800 mg. were implanted through a small incision in the back. The patient noticed unmistakable effects within a few days. During the first week he had 3 to 4 erections daily and 2 nocturnal emissions. The voice deepened somewhat, the beard became heavier and the penis increased .75 cm. in length. Two months later the muscles of the arms and legs had developed noticeably and his general strength had improved. He reported 5 to 6 erections daily, 3 nocturnal emissions a week and greater attraction toward the opposite sex. The size of the genitalia was unaltered. He had gained 3.25 lb.; the total gain in weight under implantation therapy was 16.25 lb. He had not received any other treatment, so that this gain was directly attributable to the implantations of male hormone.

In April, 1941, 5 months after the last implant, the effects had definitely 'run out.' Only partial erections occurred every 1 to 2 days and nocturnal emissions had decreased. However, the size of the gentalia had not changed; the prostate was about two-thirds normal size. The bone age was still 17 years. The patient complained of sensitivity at the site of the implant. A local area of redness and fluctuation was opened surgically and a small cavity containing necrotic and purulent material was encountered just beneath the skin. The entire area of the implant was dissected out by cautery. The tissue contained 4 pellets of testosterone which after drying weighed a total of 370 mg. Each pellet was surrounded by a yellowish capsule of fibrous tissue and a foreign-body and phagocytic reaction. Apparently this reaction had rendered nearly one-half of the 800-mg. implant ineffectual.

During a short interim of 4 weeks the patient received tablets of methyl testosterone orally in doses of 10 mg. three times daily. He felt well and gained 9 lb., to a weight level of 155 lb. Erections increased to 3 to 4 daily; each week the patient masturbated once and had nocturnal emissions twice. On May 15, 1941, sublingual administration of methyl testosterone in propylene glycol in doses of 5 mg. twice daily was begun. After 3 weeks the dose was increased to 5 mg. three times daily, and after the fourth week to 5 mg. four times daily. The patient reported that the results did not equal those obtained with the tablets. Erections decreased to two daily and nocturnal emissions ceased for 6 weeks, although the patient continued to masturbate about once a week. After 2 months the medication was changed to testosterone propionate in propylene glycol given sublingually in doses of 5 mg. four times daily. The effects after 2.5 months were similar to those brought about by the methyl testosterone. Erections occurred once or twice daily but only 2 nocturnal emissions occurred in that period of time. On Oct. 23, 1941, sublingual treatment with free testosterone in propylene glycol in doses of 5 mg. four times daily was instituted. As a result the erections increased to 2 to 3 daily, but they were not as satisfactory as those which had resulted from the oral dose.

At the time of this report the patient has been receiving testosterone sublingually for 5 months. The frequency of erections has gradually decreased to 1 every 3 to 4 days. He has continued to masturbate every 7 to 10 days, but the amount of secretion has lessened. The size of the external genitalia is unaltered. The patient has lost weight and has become somewhat depressed. He believes that he has lost some of the firmness of his general musculature and that his voice has become slightly higher in pitch. He has continued to shave once every 3 weeks. A survey of the 10 months of sublingual therapy shows that the patient apparently has lost ground in the subjective and functional sphere. The only objective change is loss of weight from 155 to 141.5 lb. However, 7 pounds of this loss occurred during one week under circumstances surrounding his marriage which he decided to consummate in spite of the regression of his condition. When he was last seen one week after his marriage, he had not achieved a satisfactory penetration.

Case 2; L.K. (U 20634). Case 3 in (1); *Case 3* in (2) with photographs. The patient was 24 years old when he was first seen in September, 1937. He had been operated upon for bilateral cryptorchidism at the age of 16; at that time the left testicle had been atrophic. The height was 71.75 in., his weight, 146 lb. He had the disproportionately long arms and legs of a typical eunuchoid. He had never shaved and his voice was high-pitched. Pubic hair was sparse and only a very few axillary hairs were present. The penis was small (length 4.75 cm.) and the scrotal content consisted of some questionable tissue in the left side. The bone age was 15 (at 24 years of age). Equine gonadotropic hormone had been administered (48 injections in 4 months) without benefit.

Testosterone propionate was given parenterally for 16 months; the total amount was 3500 mg. Thereupon the patient's voice deepened and he had occasional nocturnal emissions and practiced masturbation. The hair in the pubic escutcheon increased moderately and the axillary hair grew considerably. The length of the penis was 8 cm. (formerly 4.75 cm.) and the circumference was 10 cm. The testes were palpable; the right was bean-sized and the left was the size of a small olive. The bone age was 19 years (an acceleration of 4 years in 2 years' elapsed time). Increased mental and emotional responses as well as vigor and strength were evident. He had gained 20 lb.

In the following year (November, 1939, to November, 1940) the patient received 5 implants of methyl testosterone introduced subcutaneouslv through a large-bore needle. The dosage, given in tiny pellets, varied from 101.3 mg. to 164 mg. The improvement obtained by the parenteral method was maintained both subjectively and objectively. Libido remained unchanged for as long as nine weeks. During this period the patient married and was able to have successful intercourse as often as once a week. The length of the penis increased further, 2 cm., and the patient now shaved once a week.

In November, 1940, when the patient was 27 years old, oral therapy was instituted. For the first 4 months he received one 10-mg. tablet of methyl testosterone 3 times daily. The effect of the implant given 2 months before had begun to wane so that he had not had intercourse during the month prior to institution of oral therapy. The tablets stimulated him almost immediately; 2 days later he had erections three times a day and reported successful intercourse three times in the subsequent month. Four months after the beginning of oral therapy, the dose was reduced from 30 to 20 mg. daily to determine whether this diminished amount would suffice. A month later the patient reported that within 2 weeks of reducing the dose the frequency of erections had diminished somewhat. However, libido had remained the same. It seemed doubtful that a dose of 20 mg. daily by mouth would continue to be adequate for this patient. It was therefore again increased to 30 mg. daily. Evidently oral administration of 210 mg. a week had, in this patient, an effect equivalent to parenteral administration of 75 mg. a week. This is a ratio of not quite 3 to 1.

In May, 1941, the treatment was changed to sublingual administration of methyl testosterone in propylene glycol in doses of 5 mg. twice daily. During the subsequent 3 months the frequency of erections diminished to 3 to 4 weekly but the patient was still able to have satisfactory intercourse once each week and in general continued to feel well. The size of the genitalia did not change and the weight remained stationary. Medication was shifted to sublingual administration of testosterone propionate in propylene glycol in doses of 5 mg. twice a day and was continued on this basis for 2 months. No noticeable changes in effect occurred. On Oct. 20, 1941, therapy was changed to sublingual administration of free testosterone in propylene glycol in doses of 5 mg. twice daily. Thereupon the patient reported slight improvement of libido and general strength. Erections occurred two to three times per week. Three months later the dose was increased to 15 mg. daily.

At the time of this report the patient has received the same preparation for 5 months. He has daily erections and continues to have satisfactory intercourse every week. The genitalia have not altered in size. Since sublingual therapy was begun he has complained of sensitivity of the nipples. A small amount of glandular tissue was felt under each nipple and for a short time small amounts of fluid could be expressed. It appears that in this typical eunuchoid a dose of 15 mg. of testosterone a day sublingually is able to maintain the improved status for which 30 mg. of methyl testosterone taken orally were required. In this patient, therefore, therapy by the sublingual route appears to be more economical than by the peroral route.

Case 3; B.C., (U 4545). Case 6 in (1) with photographs; *Case 5* in (2). The patient was 17 years old when he was first seen in March, 1933. He showed characteristic evidence of preadolescent eunuchoidism with disproportionately long extremities. The height was 63.75 in, and weight 114 lb. The voice was high-pitched and he had no beard nor axillary or pubic hair. The penis was small (7 cm. in length) and the testes were the size of small olives. The prostate was barely palpable. The bone age was 15 to 17 years (at 17 years). The B.M.R. was −24 per cent. Treatment with chorionic gonadotropin, thyroid substance and androstine had had negligible effect.

In November, 1936, when the patient was 21 years of age, treatment with testosterone propionate was begun. At first 5 mg. and later 25 mg. were given 3 times each week parenterally. This plan was continued for a period of 3 years, until November, 1939. The total dose was 10,250 mg. Marked changes occurred during this time. The patient matured markedly, shaved every 2 weeks, had a moderate growth of axillary and pubic hair, and the penis had adult dimensions. Treatment then had to be discontinued for 4 months with consequent subjective and objective regression of noticeable degree. The penis shrank 2 cm. in length.

In March, 1940, implantation therapy was instituted. During the following 8 months the patient received 3 implants varying in dosage from 109.6 to 138.3 gm. Sexual stimulation and an increase in general strength returned. The patient's weight remained constant, but the penis again increased in length, from 9.25 to 12 cm.

Oral therapy was begun in November, 1940, with 10 mg. of methyl testosterone 3 times daily. This resulted in such marked sexual stimulation that on Dec. 19, 1940, the dose was reduced to 10 mg. twice daily and in February to 10 mg. daily. Two months later the patient expressed his entire satisfaction with the effects of this dose. His general strength had improved and he had gained 10 lb. during the period of oral treatment. He shaved once or twice a week. Erections occurred one to two times daily. He masturbated twice a week and experienced an occasional nocturnal emission. The external genitalia were slightly larger and of full adult size. In contrast, the prostate remained small and soft, about one-fourth normal size. The patient stated that he preferred oral to parenteral treatment, principally because it was more convenient. He also preferred oral therapy to implantations because the tablets provided a more uniform stimulus whereas the implants 'built up to a peak and then let down.'

In April, 1941, sublingual treatment with methyl testosterone in propylene glycol in doses of 5 mg. twice daily was begun. After 2 months the patient reported that the effect was comparable to that of one 10-mg. tablet of methyl testosterone taken daily by mouth. Erections occurred at first twice daily and later once daily. Each week the patient masturbated about twice and had one nocturnal emission. In June, 1941, the therapy was changed to testosterone propionate administered sublingually in doses of 5 mg. twice daily, and was continued for 2 months with comparable effect. Thereupon free testosterone in propylene glycol was administered sublingually in doses of 5 mg. twice daily. More stimulation resulted and several erections occurred every night. After 6 months the patient reported erections twice daily and emissions twice weekly. The size of the genitalia had slightly decreased. The length of the penis was 12.25 cm. (formerly 13 cm.). During the 10 months of sublingual therapy he had lost 10 lb., to 157.75 lb. however, this loss may in part be ascribed to a change in occupation which required more strenuous physical exertion. He also complained of transient soreness and secretion from the nipples during sublingual therapy. In this patient a sublingual dose of 10 mg. daily

had an effect neither greater nor less than an oral dose of 10 mg.

Case 4; J.J., (U 36521). Case 4 in (1) with photographs; *Case 4* in (2). The patient was 31 years old when he was first seen in May, 1938. He gave a history of epileptiform seizures from the age of 16, but he had had none in the preceding 2 years. He had typical preadolescent eunuchoidism with disproportionately long extremities. The height was 71 in., the weight 123 lb. The voice was high-pitched; he had a few axillary hairs and a moderate amount of pubic hair. He clipped the fuzz from his face every 2 or 3 weeks. The penis was small (length 4.5 cm.). Testes and scrotum were very small; the prostate was not palpable. The bone age was 18 years (at 31 years of age). He had been given equine gonadotropic hormone for 3 months without effect.

Parenteral administration of testosterone propionate was begun in January, 1939, in doses of 25 mg. three times a week for 1 year; the total dose was 3800 mg. Marked subjective and objective improvement resulted. He had frequent erections and practiced occasional masturbation and sexual intercourse. Other effects were increased strength and a gain in weight of 14.5 lb. The penis grew 3.5 cm. so that it now measured 8 cm. in length. The prostate enlarged to one-half normal size. The bone age advanced slightly.

In February, 1940, implantation therapy was instituted. During the succeeding 9 months the patient received 4 implants of methyl testosterone varying in size from 102.7 to 148.1 mg. The previous benefits were maintained and the stimulation from each implant lasted from 7 to 15 weeks. Libido and potentia remained about the same and the penis grew slightly larger, to 9 cm. in length.

In November, 1940, oral therapy of methyl testosterone 10 mg. three times daily, was begun. Sexual stimulation was prompt; it was noticeable in 48 hours. The patient had successful intercourse twice in the following 2 weeks and erections two and three times daily. The penis grew 1.75 cm. in length and 1.25 cm. in circumference in these 2 weeks. Five months later, on April 3, 1941, the patient had gained 5 lb. and had felt an increase in strength. The bone age had advanced to between 19 and 22 years of age. The subjective benefits previously obtained from parenteral and implantation therapy were well maintained on a dose of 30 mg. daily by mouth. No further significant change occurred in the size of the genitalia and the secondary sexual characteristics were about the same as when oral therapy was begun. The size of the prostate had not changed during the previous 8 months.

On April 14, 1941, sublingual therapy was instituted with methyl testosterone in propylene glycol in doses of 5 mg. twice daily. During 3.5 months the sexual stimulation was as before. The patient continued to have erections 2 to 3 times daily, he masturbated once or twice each week and had occasional successful intercourse. During this period the patient contemplated marriage, but the plans were cancelled when he had an epileptiform seizure at his fiancee's home the day before the projected wedding. On July 25, 1941, treatment was changed to testosterone propionate in propylene glycol administered sublingually in doses of 5 mg. twice daily. It was continued for 2 months. The effects remained about the same. On Sept. 18, 1941, therapy with free testosterone in propylene glycol in doses of 5 mg. twice a day given sublingually was begun. Sexual function continued unchanged. On Nov. 29, 1941, a specimen of spermatic fluid was obtained by masturbation. Microscopic examination did not reveal any young or mature spermatozoa. In December, 1941, the patient reported that he had occasional orgasms without emissions following masturbation. The erections had decreased to 1 or 2 a week and his condition was evidently regressing. In January, 1942, the dose was increased to 15 mg. daily. The following month he reported a slight increase in the number of erections. However, at his last visit in March, 1942, he reported only 1 to 3 erections weekly and no nocturnal or other emissions. The penis was slightly smaller than before, measuring 9 cm. in length, and he had lost 10 lb. during the 11 months of sublingual therapy. His general strength had not improved nor had hair-growth progressed. He still had occasional convulsive seizures. He expressed a preference for treatment by implantation, principally because of the greater duration of effect. In this patient, who was an example of severe eunuchodism, a daily dose of 15 mg. of testosterone administered sublingually was far less effective than 30 mg. of methyl testosterone given orally.

Case 5; F.V., (U 62077). Case 6 in (2) with photographs. This 24-year-old sandblast helper was first seen as a private patient in July, 1940. His chief complaint was lack of sexual development which had been noted since he was 13 or 14 years old. Scant pubic hair had appeared at that time and the patient had masturbated occasionally, but with the ejaculation of only a very slight amount of secretion. Axillary hair appeared at the age 18, simultaneously with a moderate spurt in body growth. Since he was 21 years of age he had not masturbated but had had nocturnal emissions every 3 or 4 months with very scant secretion. He had had a few injections of testosterone propionate at weekly intervals which had caused some erections. He had never shaved.

The patient was 66.75 in. tall and weighed 155 lb. His extremities were disproportionately long. He looked younger than this stated age and the voice was high-pitched. He had scant axillary and pubic hair and no beard or other body hair. The blood pressure was 100 mm. Hg systolic and 60, diastolic. The penis was small; it measured 4 cm. from pubic bone to tip and 6.5 cm. in circumference. The testes were small and soft; the right measured 2.5 × 1.25 cm. and the left 1.5 × 1.5 cm. The prostate was about two-thirds normal size. Laboratory investigation revealed a relative lymphocytosis and a B.M.R. of −18 per cent. Roentgenograms of the skull were normal. The bone age was 16 years (chronological age 24 years).

The patient was transferred to the University of California Hospital Clinic. On Aug. 8, 1940, he received an implant of 17 pellets of methyl testosterone, or a total of 117 mg. The effects were noticeable the next day and reached a peak of 4 to 5 erections daily 10 days later. A definite waning was noted after 5.5 weeks. In Sept. 19, 1940, a second implant was given which totalled 122.9 mg. in 14 pellets. The reaction was similar to that of the first implantation. The effect lasted 6 weeks. On Nov. 7, 1940, a third implant of 600 mg. of methyl testosterone

was placed in the subcutaneous tissues of the back. This large amount, consisting of 3 tablets of 200 mg. each, was given in order to determine whether augmented response would be obtained and whether such stimulation would be maintained for a much longer time. Two days after the implantation the patient began to have almost continuous partial priapism which lasted for a period of 7 to 10 days. The sexual stimulation gradually diminished and had subsided entirely by Jan. 24, 1941, approximately 11 weeks

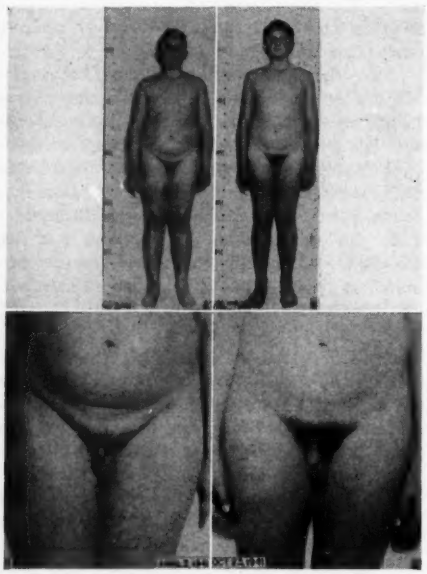

FIG. 1. *Case 6. F. R.* (U 70152): age 16 yr. 8 mo.; delayed maturity; treatment with testosterone administered sublingually. In the course of 7 months of treatment there was a growth of 2 inches in height and a loss of 10 lb. in weight, without restriction of diet. Note more masculine configuration, growth of penis and increased amount of pubic hair.

after the implantation. The patient remarked that it had definitely 'run out.' The length of the penis was 5.75 cm. (an increase of 1.75 cm.); circumference was 8.25 cm. The right testis remained the same whereas the left had enlarged from 1.5 × 1.5 to 3 × 1.5 cm. Other effects noted were occasional nocturnal emissions, increase in general strength and more vigorous growth of beard and body hair. It is interesting to note that on implantation therapy alone the B.M.R. had risen from −18 to −2 per cent.

In order to compare the effects of small and large implants with oral administration, oral therapy was begun on Feb. 6, 1941, with a dose of 30 mg. daily. Within the first 48 hours the patient experienced frequent erections which occurred daily. Four nocturnal emissions occurred within the first 3 weeks and the relaxed penis had increased 1 cm. in length. The patient had gained 3 lb.

This patient had gained 9 lb. in 2 months on oral testosterone therapy alone. During 8 months of male hormone treatment, he had gained 20 lb. and had grown 1.5 in although he was 24 years old. After 2 months of oral therapy the penis had grown slightly longer, the testes were perhaps slightly larger and the voice had deepened. The prostate was considered of normal size. The blood pressure, which had been 100/60 mm. Hg. had risen to 120/70. Although he had had considerable libido, he had refrained from masturbating because someone had told him it was 'the wrong thing to do.' He volunteered a preference for oral over implant therapy because under the former he felt stronger and experienced more frequent erections.

Sublingual therapy was begun on June 12, 1941, with methyl testosterone in propylene glycol in doses of 5 gm. twice daily. The treatment was continued for 2 months during which time the number of erections gradually diminished to 2 a week. The patient masturbated once or twice a week and had occasional nocturnal emissions. Therapy was then changed to testosterone propionate in propylene glycol administered sublingually in doses of 5 mg. twice daily. During 2 months on this therapy no apparent change occurred. On Oct. 9, 1941, sublingual administration of free testosterone in doses of 5 mg. twice a day was begun. As a result the erections increased to 3 or 4 a week; the patient continued to masturbate about twice weekly. The treatment was continued with comparable results for 2 months. The dose then was increased to 5 mg. three times daily, but not much change in effect resulted. During the 8 months of sublingual therapy the patient's general strength had remained the same and he had gained 12 lb. to a weight level of 172 lb. The genitalia were not altered in size. He continued to shave every week. The pubic hair and the hair on his legs had increased somewhat. In this patient, another example of severe eunuchoidism, a daily dose of 15 mg. of testosterone given sublingually was fairly satisfactory although subjective sexual stimulation was not as pronounced as from 30 mg. daily of methyl testosterone given orally.

Case 6; F.R., (U 70152). When the patient was first seen on March 22, 1941, he was 16 years, 8 months old. His complaints were obesity and retarded sexual development. Pubic hair appeared at about the age of 15 years but the penis did not increase in size. The patient had never shaved. However, he had daily erections and masturbated occasionally.

The patient was 65.5 in. tall and weighed 170.25 lb. unclothed. He was rather obese about the abdomen and had full rounded thighs (fig. 1, A). He had no beard or axillary hair and very little pubic hair. No prostatic tissue could be palpated. The testes were of normal size. The penis measured 4 cm. in length and 6.5 cm. in circumference (fig. 1, C). The B.M.R. was −19 per cent. Plasma cholesterol was 119 mg. per cent. The bone age was 14 years (chronological age, 16 years, 8 months). The I.Q. was 90.

On April 7, 1941, sublingual administration of testosterone propionate in propylene glycol in doses of 10 mg. daily was initiated. By May 29, 1941, the pubic hair had slightly increased, but since this might have occurred naturally the dose was increased to 25 mg. daily. On July 10, 1941, the medication was changed to methyl testosterone in propylene glycol administered sublingually in doses of 25 mg. daily. During 6.5 months of sublingual

testosterone therapy the patient lost 9.5 lb. without dieting and grew 2 in. in height (fig. 1, B). The pubic hair increased markedly and axillary hair appeared. The penis increased 3 cm. in length and 3 cm. in circumference (fig. 1, D). Although no change in subjective sensations occurred, the I.Q. increased from 90 to 116.

This patient had received no treatment whatsoever besides sublingual testosterone. The striking improvement in growth, the loss of weight, the change of figure, the increase in size of genitalia and the augmentation of the secondary sex characteristics may be attributed to the male hormone therapy. Although the patient probably would have matured eventually without treatment, his development would have been delayed for a year or two, if not longer. Provoking and hastening the maturity has done no harm and has spared the patient much anguish and embarrassment.

Case 7; L.A., (*U 78157*). The patient was first seen on Nov. 6, 1941, at which time he was 21 years, 4 months old. He complained of bilateral cryptorchidism, lack of sexual development, anosmia since birth and a speech defect. He had developed slowly, had not been able to walk until the age of 3 years and had begun to talk soon thereafter. When he was 1 year old he had had an infection accompanied by convulsions. He had not attended school before he was 8 years of age and at 13 years he had reached only the third grade. Therefore he had been sent to a corrective school from which he had derived little benefit. With considerable prodding he finally had finished high school at the age of 20 years. When he was 11 years old he had been operated upon for cryptorchidism without success. At the age of 17 years he had received a series of injections once or twice a week for 1 year; the only result had been slight growth of pubic hair. He had never shaved and had never had erections or ejaculations.

The patient had narrow shoulders and disproportionately long arms and legs. His abdomen was protuberant and he had marked genu valgus. The height was 66.75 in. and the weight 144.5 lb. unclothed. His span was 70 in. and the lower measurement, from pubis to soles, 36.75 in. He had sparse pubic and axillary hair and no beard. The penis measured 3.5 cm. in length and 4.5 cm. in circumference. The right testicle was pea-sized and situated at the external inguinal ring. The left testicle was not felt (fig. 2, C). The I.Q. was 75. The B.M.R. was −10 per cent. By x-ray study the bone age was estimated at 15 to 16 years, a retardation of 5 to 6 years. The sella turcica was normal.

Sublingual administration of free testosterone in propylene glycol in doses of 20 mg. daily was begun on Nov. 13, 1941. After 3.5 months the right testis had increased slightly in size and the left had become definitely palpable in the inguinal canal. The patient was experiencing almost constant priapism. He had not masturbated nor had he had ejaculations. The penis had increased 2 cm. in length and 1 cm. in circumference (fig. 2, D). Since the I.Q. had remained approximately the same, namely 76, it was considered prudent to discontinue treatment rather than to risk producing a behavior problem in a mentally deficient individual.

This eunuchoid of 21 years of age received only free testosterone sublingually. Both subjective and objective improvement were manifest. In view of previous experience with similar degrees of gonadal deficiency, it seems to us doubtful that 20 mg. of methyl testosterone daily administered orally (that is, swallowed) would have produced as much advance in sexual maturity. Probably at least double this dose would have been required to achieve the same result.

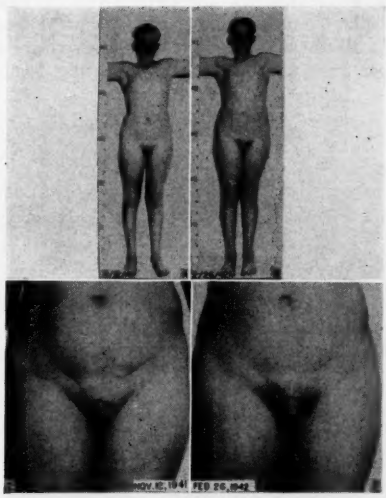

FIG. 2. *Case 7. L. P. A.* (78157): age 21 yr.; pre-adolescent eunuchoidism with cryptorchidism; treatment with testosterone sublingually. In the course of 3 months of treatment there was a growth of 1¼ in. in height and a gain of 7 lb. in weight. Note growth of penis and scrotum and increased amount of pubic hair.

Case 8,[2] *S.S.*, (*U 72982*). The patient was first seen on June 9, 1941, at the age of 29.5 years. He complained of lack of sexual development. The penis had always been small. He had experienced erections occasionally and had attempted masturbation but had never had an ejaculation.

The patient was short (height, 62.5 in.) and looked like an elderly boy. He weighed 130 lb. and was plump about the waist (fig. 3, A). He had no beard. The pubic escutcheon was relatively sparse and of feminine type, and the axillary hair was scant. The genitalia were infantile; the scrotum was empty; the prostate was not palpable. The penis measured 2.5 cm. in length and 4.5 cm. in circumference (fig. 3, D).

Sublingual administration of testosterone propionate in propylene glycol in doses of 12.5 mg. daily was begun on June 19, 1941. During the subsequent 3 months the patient noticed occasional twinges of pain in the right inguinal region, which may have been caused by beginning descent of the testes. In addition he had daily erections and by the third month, occasional emissions. After 7 months of treatment, Jan. 8, 1942, the penis measured 3.5 cm. in

[2] This patient was observed by Dr. Evelyn Anderson who has kindly permitted us to include this case in our series.

length and 6.5 cm. in circumference (fig. 3, E). He still had daily erections and occasional ejaculations. At this time medication was changed to free testosterone in propylene glycol given sublingually in doses of 12.5 mg. daily. When the patient was seen on March 2, 1942, he had had no medication for 2 weeks. He thought the penis had regressed; however, measurements were the same as on January 8. He was last seen on April 9, 1942. At that time the penis measured 5.5 cm. in length and 7 cm. in circumference, which represents a growth of 3 cm. in length in 9.5 months of sublingual therapy. Of equal importance was the descent of the left testis into the scrotum and of the right testis to the external inguinal ring. Each testis

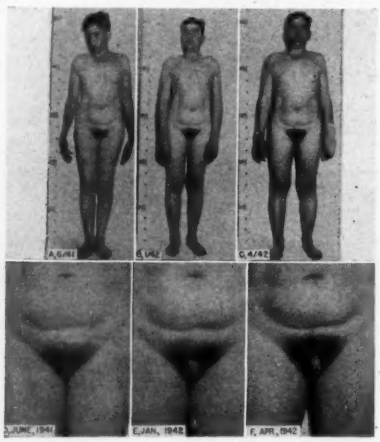

FIG. 3. *Case 8. S. S.* (U 72982): age 29.5 yr. Severe sexual retardation with cryptorchidism; treatment with testosterone administered sublingually, 12.5 mg., daily. Note gain of 15 lb. in weight, growth of penis and increased amount of pubic hair. Left testis descended into scrotum, right testis to external ring.

was about the size of a peanut. The pitch of the patient's voice had deepened markedly.

This patient, who was almost 30 years old when treatment was begun, was severely retarded in both primary and secondary sex characteristics and had bilateral cryptorchidism. Sublingual administration of testosterone in doses of only 12.5 mg. daily was remarkably effective both subjectively and objectively (the latter is evident in the photographs). Previous experience in comparable cases convinces us that at least 4 times this amount daily would have been required to achieve equivalent improvement if the treatment had consisted of oral ingestion of methyl testosterone.

Case 9; C.R., (U 38241): The patient, a 49-year-old man, was first seen on March 29, 1941. His chief complaint was diminished sexual development. In 1938 he had suffered from alcoholic polyneuritis which was severe enough to cause foot drop and slight optic atrophy. There was some residual loss of vision but the other functions were fully recovered. At about the age of 17 years, a small amount of pubic hair as well as 20 to 30 hairs in each axilla had appeared. All the axillary hair and most of the pubic hair had fallen out a few years before we saw the patient. When he was about 30 years old, the 'peach fuzz' which had been on his forearms disappeared. At about the same time he had received some type of 'gland injections' over a 1-year period which had produced no change in his condition. Since he had never been strong enough to do heavy manual labor, he had worked as a cook or as a galley man on boats. In his association with seamen he had often followed the crowd ashore and had visited prostitutes. Although he had been able to force erections he had never had an ejaculation.

The patient was a relatively short man (height 65 in.) without beard and with marked wrinkling of the skin of his face (fig. 4, A). The outer ends of the eyebrows were very thin. Axillary hair was absent and there were only a few pubic hairs. The voice was not high-pitched. He weighed 153.25 lb. unclothed. He had a somewhat obese trunk and fairly marked gynecomastia. The penis measured 5.5 cm. in length and 6 cm. in circumference. The scrotum was small and retracted and contained 2 testes about the size of small olive pits (fig. 4, C and E). The B.M.R. was −7 per cent. Plasma cholesterol was 165 mg. per cent. The glucose tolerance curve was normal.

On April 10, 1941, testosterone propionate dissolved in propylene glycol (25 mg. per cc.) to be taken sublingually in doses of 0.1 cc. (2.5 mg.) 4 times daily, was prescribed. However, the patient took it only 3 times daily. On May 24, 1941, the error was discovered and the dose was increased to a total of 10 mg. daily. During this period no objective change occurred but the patient had 2 to 3 erections each night. By Sept. 18, 1941, the pubic hair had definitely increased (fig. 4, F). Nevertheless, the dose seemed inadequate and was increased to 25 mg. daily. On Oct. 10, 1941, 1 month later, the patient had had 2 nocturnal emissions; the penis measured 6 cm. in length and 8 cm. in circumference (fig. 4, G). Medication was changed to free testosterone in propylene glycol administered in doses of 25 mg. daily by the sublingual route. Almost immediately the patient complained of extreme restlessness and insomnia. Erections increased to 3 to 4 daily and 2 further emissions occurred in the following month. On Nov. 27, the penis measured 6 cm. in length and 8.5 cm. in circumference.

During 6.5 months of sublingual therapy with testosterone propionate, slow regrowth of pubic hair occurred and for the first time in his life the patient became conscious of libido. The penis increased 2 cm. in circumference. The tardy progress probably can be attributed to inadequate dosage. After about 5 months of treatment the patient's strength increased to such an extent that he was able to work as a stevedore. During 1 month of sublingual therapy with free testosterone there was more striking increase in pubic hair and libido. The penis increased 0.5 cm. in length and circumference.

Several circumstances interfered with this patient's therapy, so that he had no testosterone at all during January, February and March, 1942. Erections diminished in frequency but he continued to feel well. On Mar. 26, 1942, the length of the penis was 5 cm. and its circumference 8.5 cm. On this date sublingual free testosterone

therapy was resumed in doses of 25 mg. daily. Two weeks later, Apr. 19, the length of the penis had increased 1.5 cm. and the circumference 1 cm. (fig. 4, H). The patient was having 3 to 4 erections daily and felt generally stronger and more vigorous.

This patient is an example of idiopathic late adult hypogonadism. Both subjective and objective improvement was obtained from sublingual testosterone therapy. For several months, while the patient was in Alaska, he could not be kept under observation and the dosage was insufficient. From previous experience we are inclined to believe that 25 mg. of testosterone propionate administered parenterally three times a week would have been considerably more effective than the sublingual dose. Nevertheless, this clinical experiment with sublingual therapy produced photographically demonstrable improvement.

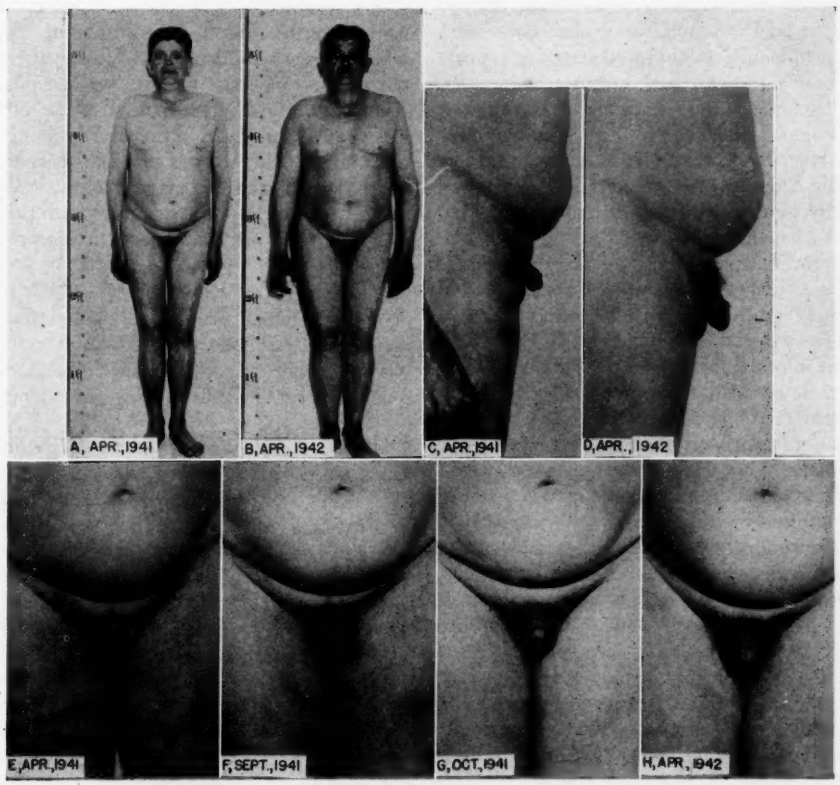

FIG. 4. *Case* 9. C. R. (U 38241): age 49 yr. Idiopathic, late adult hypogonadism. Treatment with testosterone administered sublingually, 10 mg. daily, 4/41 to 9/41; 25 mg. daily 9/41 to 4/42, except for Jan., Feb., and most of March, 1942. Note marked gain in weight and slight growth in height (at 49 years of age); increase in size of penis and growth of pubic hair.

SUMMARY AND DISCUSSION

The purpose of this investigation was to determine whether various testosterone compounds administered under the tongue (sublingually) would achieve the following results: *a*), maintain the improvement previously produced and maintained in cases of severe eunuchoidism by other modes of testosterone therapy, namely by administration of testosterone propionate parenterally, by implantation of methyl testosterone pellets subcutaneously and/or by administration of methyl testosterone tablets perorally; *b*), initiate an improved sexual status subjectively and objectively in hypogonad individuals who had not previously received any form of testosterone therapy; *c*), reveal the advantages or disadvantages economically and otherwise of such sublingual administration as compared to parenteral, implantation or oral administration; and *d*), ascertain whether the methyl ester, the propionate or free testosterone (each dissolved in propylene glycol so that 0.2 cc. contains 5 mg.) is the most efficient. We believe that our experience in the 9 cases reported provides an adequate answer to these four considerations.

The effectiveness of testosterone compounds administered sublingually as a maintenance regime was

tested in 5 patients all of whom had been typical examples of severe preadolescent eunuchoidism and who had been exceedingly immature at the ages of 24, 24, 21, 31 and 24 years, respectively. At the time sublingual therapy was initiated they had been vastly improved by other forms of testosterone therapy. They had reached the ages of 25, 28, 26, 34, and 25 years, respectively.

A comparison of the results of sublingual and peroral therapy was made because peroral therapy had been found the simplest and most convenient means of maintaining an improved status in eunuchoids. In *case* 3, the patient's status remained the same on a sublingual dose of 10 mg. daily as it had been on a similar oral dose. In *case* 1, 20 mg. daily given sublingually were not as effective as 30 mg. given orally had been. In *case* 4, 15 mg. daily given sublingually were far less effective than 30 mg. given orally had been. In *case* 5, 15 mg. daily given sublingually proved satisfactory although it was not as stimulating as 30 mg. given orally had been. In *case* 2, 15 mg. daily given sublingually accomplished the same results as the oral dose of 30 mg. had done. For the patient in *case* 2 therapy by the sublingual route was the more economical since one-half the amount of testosterone required for the oral route produced the desired effect. With this exception sublingual therapy offered no significant advantage over peroral therapy. Furthermore, these 5 patients who had had experience with other forms of testosterone therapy disliked the sublingual method because it was unpleasant and inconvenient.

The protocols and photographs of the patients in *cases* 6, 7, 8 and 9, none of whom had been treated previously with testosterone, clearly demonstrate that sublingual administration of testosterone compounds produces striking improvement with decidedly smaller dosage than would be required to accomplish equivalent results by swallowing tablets. Roughly, one-third the amount used orally will suffice by the sublingual route. This factor may be important from the economic standpoint. However, we desire to point out that 25 mg. of testosterone propionate injected intramuscularly three times a week would accomplish similar improvement more rapidly than 20 to 25 mg. daily given sublingually. Furthermore, a previous report (1) indicated that by the subcutaneous implantation of testosterone pellets only one-fifth the amount used parenterally is required.

Sublingual therapy seems to us to possess only one advantage which does not, however, apply uniformly: namely, a smaller dose is effective than by peroral therapy. Objections to the sublingual method, at least when testosterone compounds are dissolved in propylene glycol, are the unpleasant taste, the tendency to salivation and the manifest inconvenience of holding the mouth open and the head back for several minutes without swallowing the solution. A patient could hardly be expected to submit to this procedure oftener than 5 times a day. Since the maximum dose of hormone in concentrations now available, which is at all practicable, is 0.2 cc., or 5 mg., the largest amount of hormone that can be administered sublingually in 24 hours is 25 mg.

No appreciable difference was evident between methyl testosterone and testosterone propionate when they were administered sublingually, but free testosterone in equal weights was definitely more effective than either the methyl or the propionate. All 9 patients included in this series volunteered this observation. The obvious explanation is that more androgenic substance exists in free testosterone than in an equal weight of the esters in which part of such weight is taken up by the methyl or propionic acid radicle.

CONCLUSIONS

1. Testosterone propionate, methyl testosterone and free testosterone, each dissolved in propylene glycol so that 0.2 cc. contained 5 mg., were administered sublingually in daily doses ranging from 10 to 25 mg.

2. Five typical eunuchoids whose condition previously had been improved and who had been successfully maintained by parenteral, implantation and/or oral administration of testosterone compounds, continued their improved states on sublingual testosterone. In only 1 of the 5 cases was the sublingual mode of therapy more economical in milligrams required than the peroral route. All the patients preferred swallowing tablets to dropping a solution under the tongue.

3. Four hypogonadal patients who had not previously received any testosterone therapy derived striking benefits subjectively and objectively from the the sublingual administration of testosterone compounds. Larger oral doses of methyl testosterone would have been required to accomplish equivalent results.

4. Sublingually, free testosterone was more effective than either methyl testosterone or testosterone propionate.

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Appraisal of Estrogenic Activity by the Vaginal Glycogen Index:

A Comparison of Oral and Parenteral Estrone

[Vaginal Glycogen Index]

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IN A RECENT publication (1) describing the iodine vapor method of demonstrating glycogen in human vaginal smears, this procedure[1] was proposed as a simple and rapid means of indicating human estrogenic response, either physiological or artificially induced. The rapidity with which a glycogen increase could be demonstrated in cases of advanced menopausal atrophy after estrone was administered parenterally and vaginally, prompted use of the test for appraising the activity of estrone by the oral route. The need for objective evidence in the human female of the comparative potency of orally and parenterally administered estrone is evident from the widely divergent data obtained from animal experiments which show "once more the difficulty of interpreting the therapeutic effectiveness of estrogens on the basis of laboratory data."(2).

Although glycogen is not always totally absent from the vaginal mucosa, even in advanced senility (3), its relative deficiency in the menopausal state as compared to the reproductive period is usually quite evident. Varying degrees of residual ovarian activity, estrogen elaboration by other endocrine organs (adrenal), or access of estrus-inducing substances from extrinsic sources, may account for differences observed in the menopausal mucosa. The factors which may govern the highly variable degree of vaginal involution during senility are important considerations of the menopause in general, and of atrophic vaginitis in particular.

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[1] Iodine vapor method. *a). Preparation of smears.* A moistened cotton applicator is inserted into the vagina and twirled lightly (one complete rotation) against the vaginal wall. The cotton end of the applicator is then rolled lengthwise over the surface of a clean glass side. By rolling, rather than rubbing, a uniformly thin film of cells, with minimal clumping and cell distortion, results. The film dries almost immediately and may be stained at once.

b). Staining of smears. Staining is accomplished simply by laying the slide, face down, over a shallow dish containing a small amount of Lugol's solution. Iodine vapors which arise insensibly from the solution suffice to stain the glycogen-containing cells in 2 or 3 minutes. Microscopic examination may be carried out immediately. Although such stains fade in 24 to 48 hours, re-staining (by the same method) may be carried out repeatedly if later examinations are desired.

MATERIAL AND METHODS

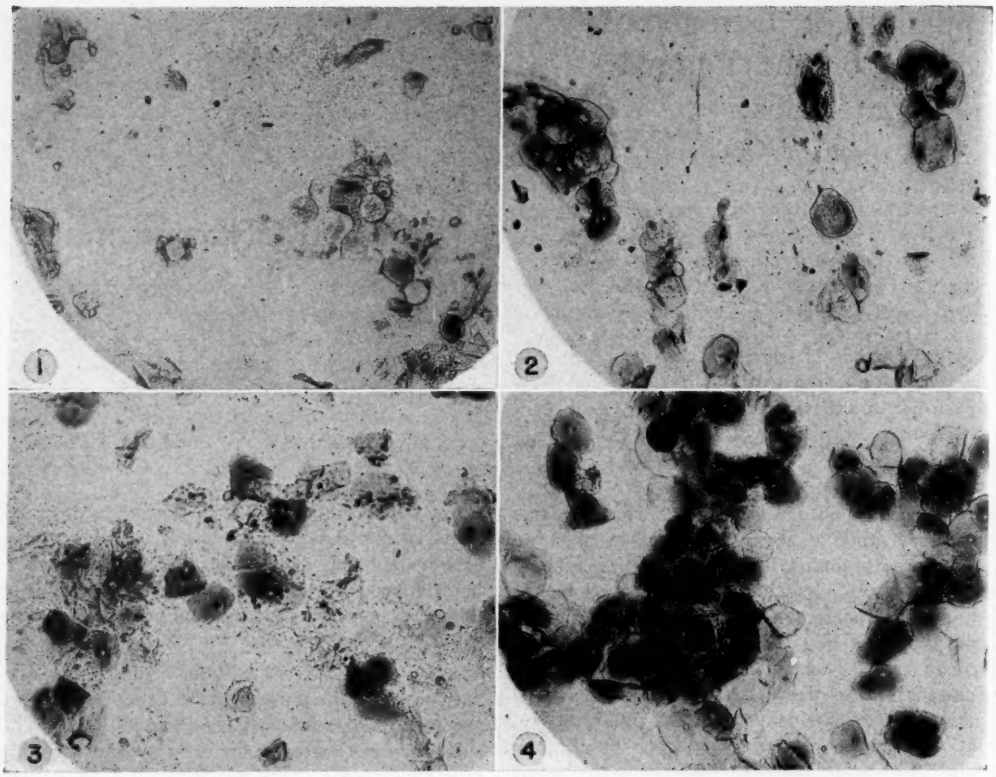
In selecting the ten subjects of this study, a large group of menopausal women was investigated. The subjects were selected on the basis of vaginal atrophy characterized by advanced degrees of glycopenia, since more glycogen indicates that some degree of estrogenic activity might still be present. Preparations for determining the glycogen index were graded as follows.

Grade 1. Complete glycopenia. In extreme degrees, this grade is also distinguished by marked cytopenia. The smear shows only small yellow cells of varying sizes and shapes and large amounts of amorphous cellular debris (fig. 1).

Grade 2. Smears of this grade show a greater abundance of cells than those of *grade 1*. Iodine vapor staining depicts glycogen in irregular brown deposits at the cell margins or scattered irregularly throughout the cytoplasm, 'mottled cells.' Diffusely stained brown cells, usually of the small round variety, 'deep cells', may also be present in small numbers. A large number of glycopenic yellow cells is also present (fig. 2).

Grade 3. A further increase in cell numbers is noted in this grade. The cells are larger and more regular in outline. The majority are stained diffusely throughout the cytoplasm. They have a light brown color. Non-iodophilic yellow cells are also present in abundance (fig. 3).

Grade 4. This grade is easily recognized by the presence, almost exclusively, of large, flat, deeply stained, brown iodophilic cells present singly or in clumps. This grade represents maximal estrogenic effect and corresponds to the smear of the normal proliferative phase (fig. 4).



VAGINAL SMEARS STAINED FOR GLYCOGEN. Fig. 1, Grade 1. Fig. 2, Grade 2. Fig. 3, Grade 3. Fig. 4, Grade 4.

Subjects. Ten menopausal women ranging in age from 44 to 66 years, were selected from the wards of the Tuberculosis Division of Herman Kiefer Hospital, on the basis of advanced glycopenia (*grades 1* and *2*).

Patient	Age	Menopause	Vaginal Smear, Glycogen Index
1, M.N.	55	Irradiation menopause, 1929	*Grade 2*
2, M.S.	58	Natural menopause, 1933	*Grade 1*
3, M.P.	44	Natural menopause, 1940	*Grade 2*
4, R.S.	59	Natural menopause, 1930	*Grade 2*
5, M.T.	66	Natural menopause, 1923	*Grade 1*
6, V.A.	64	Natural menopause, 1926 (?)	*Grade 2*
7, G.H.	48	Natural menopause, 1939	*Grade 2*
8, D.G.	56	Natural menopause, (?) yr.	*Grade 1*
9, J.G.	66	Natural menopause, 1926	*Grade 1*
10, P.L.	59	Natural menopause, 1936	*Grade 1*

All were patients with various stages of advanced tuberculosis.

Materials. The estrone preparation used for oral administration consisted of gelatin capsules containing 0.5 mg. of crystalline estrone[2] dissolved in corn oil. Each capsule represented an estrogenic potency of 5000 international units.

The estrone used for parenteral administration consisted of 5.0 mg. ampules of crystalline estrone in aqueous suspension. Each ampule represented an estrogenic potency of 50,000 I.U.

Dosages. To compare the rapidity and the duration of effectiveness of the oral and parenteral estrone preparations prescribed, identical weighed amounts were given at different times (in six instances to the same patient) by both routes of administration. The amounts ranged from 5.0 to 15.0 mg., given in divided doses, over a five-day period, as well as in single doses, according to the following plan.

Method. Daily vaginal smears were made during each of the twenty observation periods, from the time of treatment until the vaginal effect had subsided, as indicated by regression of the smear to the

[2] The estrone preparations employed in this study were supplied through the courtesy of Parke, Davis and Company, Detroit, Mich.

Estrone, Orally	Estrone, Parenterally
Total amount given in single dose	Total amount given in single injection
5.0 mg.	5.0 mg.
7.5 mg.	7.5 mg.
10.0 mg.	10.0 mg.
12.5 mg.	12.5 mg.
15.0 mg.	15.0 mg.
In 5 equal daily doses	In 5 equal daily injections
5.0 mg.	5.0 mg.
7.5 mg.	7.5 mg.
10.0 mg.	10.0 mg.
12.5 mg.	12.5 mg.
15.0 mg.	15.0 mg.

pre-treatment grade. Smears were stained by the iodine vapor technique and graded according to the system described above.

To permit comparison of the oral and parenteral effects of equal dosage in the same subjects, *patients* 1 to 5 were given equal amounts (at different times) by both routes as single doses. *Patient* 6 received identical amounts by both routes, in divided doses. Equal amounts by both routes, in divided dosage, were given to *patients* 7 and 1; 8 and 3; 9 and 10; and 10 and 12. This plan was followed in order to determine the effects of individual susceptibility, 'estrogen sensitivity and estrogen resistance' (5), and the clinical status upon the resulting curves. It is to be noted that while all of the patients of this series had advanced tuberculosis, only *patients* 2 and 5 were in critical condition.

RESULTS

The results of this study are shown in tables 1 and 2, which permit comparison of the vaginal responses to oral and parenteral estrone administrations in graduated amounts as *a*), single doses, and *b*), divided doses over a 5-day period.

a). *Single doses* (*table* 1). Increases in vaginal glycogen were obtained in all instances after oral as well as after parenteral estrone administration. Maximal responses (*grade* 4) were attained more rapidly after oral administration (average 5.4 days) than after parenteral injection (average 8.6 days). Maximal reaction after oral administration was never sustained longer than for 2 days, whereas comparable amounts injected maintained this effect for as long as 14 days. The failure of large oral doses to provoke prolonged reactions is undoubtedly due to lack of assimilation or through excretory loss from the gastrointestinal tract. Excretion studies (urine and feces) to determine the proportion of ingested estrone lost in this manner were not made.

The effects of individual susceptibility and concomitant disease are shown in *patients* 2 and 5. *Patient* 2 had reached the terminal stages of generalized tuberculosis. Studies with single oral and parenteral administrations (7.5 mg. each) and, finally, 150. mg. in five injections (table 2) showed progressively less response with approaching exitus. It is to be noted, however, that the curves obtained for identical amounts by the two routes are strikingly similar. *Patient* 5, who had repeatedly shown prolonged maximal responses to estrone by both routes, showed a less sustained response after 15 mg. (single dose) given parenterally than did others with smaller amounts. Her death at the conclusion of this trial was preceded by withdrawal bleeding.

b). *Divided doses*, (*table* 2). Increases in vaginal glycogen were obtained in all instances and by both routes. Oral administration of estrone in divided doses produced maximal reaction as rapidly (average 6.2 days) as did the parenteral method (average 7 days). Sustained maximal effects with divided

TABLE 1. GRADED RESPONSES IN VAGINAL GLYCOGEN INDEX TO ESTRONE GIVEN IN SINGLE DOSES

Route of Administration	Patient Number	Estrone mg.	Grade of Vaginal Glycogen Index on Days 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
Oral	1	5.0	**2 2** 2 2 3 3 4 4 3 3 3 3 2 3 2 2 2 2 2 2
Parenteral	1	5.0	**2 2** 2 2 2 2 2 3 1 2 4 4 4 4 4 4 4 4 4 3 3 2 3 2 2
Oral	2	7.5	**1 1** 1 3 2 3 3 4 4 3 2 3 3 2 2 1 1 1 1
Parenteral	2	7.5	**1 1** 1 1 2 1 2 2 3 3 2 3 3 4 3 2 3 2 1 1 1 1 1 1
Oral	3	10.0	**2 2** 2 3 4 3 3 2 2 2 2 2 2 2 2 2 2 2 2
Parenteral	3	10.0	**2 2** 2 2 3 4 4 4 4 4 4 3 4 4 3 3 1 1 1
Oral	4	12.5	**2 2** 3 2 2 3 4 4 3 3 3 3 2 1 2 2 2 2 2
Parenteral	4	12.5	**2 2** 2 2 2 1 3 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 3 2 3 2 2
Oral	5	15.0	**2 2** 3 2 4 4 3 3 2 2 2 1 1 1 1
Parenteral	5	15.0	**1 1** 1 1 2 2 2 3 4 4 4 4 3 3 2 2 3 (Exitus)

Figures in boldface represent grade of glycogen index on day of treatment.

TABLE 2. GRADED RESPONSES IN VAGINAL GLYCOGEN INDEX TO GRADUATED AMOUNTS OF ESTRONE GIVEN IN DIVIDED DOSES

Route of Administration	Patient Number	Estrone, mg.	Grade of Vaginal Glycogen Index on Days 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Oral	6	5.0	**2 2 3 4 4 4** 4 4 4 4 4 3 3 4 3 3 3 3 3 2 2
Parenteral	6	5.0	**2 2 2 3 3 3** 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 2 3 3 3 2 2
Oral	7	7.5	**2 1 2 2 2 3** 3 4 4 4 3 3 2 3 2 2 2 2 2 2
Parenteral	1	7.5	**3 3 2 1 3 4** 4 4 4 4 4 4 4 4 4 4 3 3 3 3 2 2 3 2 2 2 2
Oral	8	10.0	**1 1 1 1 1 2** 3 4 4 3 1 1 1 2 1 1 1 1 1 1
Parenteral	3	10.0	**1 1 2 2 2 3** 3 4 4 4 4 3 3 3 1 1 1 1 1 1 1 1 1 1
Oral	9	12.5	**1 2 2 2 3 3** 4 4 4 4 3 3 3 2 2 3 2 2 2 2 2 1 1
Parenteral	10	12.5	**2 1 1 2 1 3** 3 4 4 4 4 3 1 3 3 2 1 2 2 2 1 1 2 1 1 1
Oral	10	15.0	**1 1 2 2 2 2** 2 3 3 4 4 4 4 4 3 3 2 2 1 1 1 1 1
Parenteral	2	15.0	**1 1 1 1 2 2** 3 2 2 2 2 1 (Exitus)

Figures in boldface represent grades of glycogen index on days of treatment.

dosage were more nearly equal than were those obtained from single doses. This difference is probably explained by diminished excretory loss. *Patient 6*, a highly estrogen sensitive subject, showed remarkably prolonged maximal reactions to both methods of administration. All subjects of this group (with the exception of *patient 2*) were in reasonably good condition. The corresponding curves for oral and parenteral administration are closely parallel with the one exception noted (2).

Toxicity. No toxic manifestations (nausea, vomiting) resulted from the oral administration of estrone, nor were any untoward effects noted upon the existing tuberculosis. No attempt was made to correlate vaginal smear changes with the effects of therapy upon menopausal symptoms.

SUMMARY

A group of 10 menopausal women with advanced vaginal atrophy, as indicated by marked glycopenia, received graduated doses of estrone by oral and parenteral administration. The effects of identical amounts, given in single or equally divided doses, were determined from daily vaginal smears stained for glycogen by the iodine vapor method. Evidence is presented which indicates that oral administration of estrone induces vaginal glycogen increases identical with those following parenteral administration of the same amounts. Maximal vaginal effects were obtained more promptly after oral than after parenteral administration. More prolonged effects were obtained from divided daily doses than from single large amounts when given by mouth. Lack of assimilation through excretory loss from the gastrointestinal tract is offered as an explanation of the lack of greater effectiveness of large oral doses. Parenterally administered estrone in single doses exerted a less prompt, though more prolonged effect; when equal amounts were given in divided doses the sustained action by both routes was more nearly equal. Variations of individual susceptibility and the influence of concomitant disease appear to influence the intensity of the vaginal glycogen response. No toxic effects (nausea, vomiting) were noted in any patient after oral administration.

CONCLUSIONS

1. Vaginal glycogen content, as demonstrated by the iodine vapor method of staining vaginal smears, is a sensitive index of estrogenic activity in the human subject.

2. Estrone when given orally is highly effective in augmenting the glycogen content of the vaginal mucosa.

3. Estrone is neither destroyed in the gastrointestinal tract nor sufficiently altered in its metabolism to interfere with its estrogenic effect upon the vaginal epithelium.

4. The promptness with which estrogenic effect follows the administration of estrone by mouth, and the ability of the oral route to sustain maximal effects by daily doses, suggest that this method can supplant parenteral injections in estrogen therapy.

5. Lack of toxic reactions in this series suggests the use of oral estrone, especially when synthetic products are not tolerated.

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Glycogen Studies on Human Endometrium:

Correlation of Quantitative Chemical Estimation and the Qualitative Demonstration by Histological Methods

[Endometrial Glycogen]

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The quantitative estimation of glycogen in the endometrium was first made by Van Slyke and Chen (1) in 1936, using the female macaque. They stated that there was an increase in glycogen in the differentiative stage over that of the proliferative stage, noting that in the proliferative stage the endometrium contained 0.3 gm. per cent, the differentiative phase 0.53 gm. per cent of glycogen and that on the first day of ovulatory menstruation there was an even slightly higher increment.

Zondek, in 1940 (2, 3) noted the same relationship in human endometrium. He reported 0.38 gm. per cent in the proliferative phase, 0.437 in the interval phase, and 0.427 gm. per cent of glycogen in the differentiative stage.

Randall and Power, in 1942, (4) estimated the glycogen content of human endometrium taken by curettage; they noted in the late proliferative phase an average of 0.171 gm. per cent, in the early differentiative phase, an average of 1.09, and in the late differentiative phase, an average of 0.71 gm. per cent of glycogen.

In order to investigate further these slightly divergent results and to correlate, if possible, the amount of chemically demonstrable glycogen for a given sample of endometrium with that shown by histological methods, the following investigation was undertaken.

Methods

Thirty-three specimens of human endometrium were analyzed quantitatively for the glycogen content and corresponding blocks of tissue were stained for glycogen and controlled by mucin staining in serial sections. These specimens were furnished from operative cases in which hysterectomy was done and the whole uterus was available. This afforded ample material for chemical and histochemical studies.

The uterus as obtained from surgery was immediately opened and blocks of the endometrium for the histochemical procedures fixed in absolute alcohol. The rest of the endometrium was carefully scraped from the myometrium with a dull spoon, care being used not to include any myometrial tissue. This was immediately transferred to the freezing microtome and frozen solid in a stream of carbon dioxide, chipped off into a tared watch glass and weighed. After weighing, the frozen tissue was transferred to a 50 cc. Erlenmeyer pyrex flask containing 5 cc. of 75 per cent potassium hydroxide, shaken well, and placed on the boiling water bath under a cold water reflux condenser for 3 hours. At the end of this time the sample was neutralized with concentrated hydrochloric acid, and 5 cc. of 2.2 per cent hydrochloric acid was added. The conversion was allowed to act for 3 hours.

At the end of this time the sample was again neutralized with 0.275 per cent sodium hydroxide and the glucose determination carried out according to the technic of Miller and Van Slyke (5). Aliquots whose titration showed no glucose were tested for carbohydrate by the phenlhydrazine hydrochloride reaction and the resorcin hydrochloride test for simple sugars.

The blocks of endometrium for histochemical determinations were fixed in absolute alcohol, and successively transferred to 80 per cent alcohol, acetone and paraffin. Serial sections were mounted, one series being stained with Delafield's hematoxylin and Best's carmine for glycogen, and the other with Delafield's hematoxylin and Mayer's mucicarmine for mucin.

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The phases of endometrial development in the various specimens were dated from the first day of menstrual flow in conformity with the terminology used by Zondek and Stein (2), and by Randall and Power (4). The stage of active regeneration following the menstrual flow was designated as proliferative. The stage immediately following this, in which there appears histologic evidence of glycogen formation, has been designated as the interval stage; this pattern is identical with that of endometrial development which is sometimes designated as ovulatory. The stage of distinct post-ovulatory differentiation follows this interval stage. Further descriptive limitations may be placed on these various stages by applying the terms early, mid or late.

The position of stained glycogen in the epithelium of the endometrial gland was designated by its location relative to the nucleus of the individual epithelial cell. The first or earliest position was at the base of the cell adjacent to the basement membrane, in which position the glycogen apparently displaced the nucleus toward the central position of the cell. Such glycogen was designated as basal. Increasing accumulations of glycogen were found to extend toward the distal or lumenal end of the cell, occupying a position lateral to the nucleus, and were designated as being in the transitional position. Later this glycogen accumulated at the lumenal or distal portion of the epithelial cell and the nucleus again assumed a basal position. Small amounts of the lumenal glycogen were occasionally extruded as globules into the lumen of the gland.

TABLE 1. CHEMICAL DETERMINATION AND HISTOLOGICAL ESTIMATION OF GLYCOGEN IN HUMAN ENDOMETRIUM

Endometrial Stage	Chemical Determinations				Histological Estimations			
	Weight sample, gm.	Glycogen mg. %	P	R	Amount of glycogen stained in		Amount of Mucin Stained in	
					Cells	Lumen	Cells	Lumen
Early proliferative	0.140		0	0	0	0	0	3+
Early proliferative	0.059	88			0	0	0	3+
Early proliferative	0.542	240			0	0	0	1+
Early proliferative	0.408	63			0	0	0	1+
Early proliferative	0.632	114			0	0	0	1+
Early proliferative	0.632	114			0	0	0	1+
Early proliferative	0.345	336			0	0	0	1+
Mid proliferative	0.307	186			1+, basal	0	0	3+
Mid proliferative	0.830		0	0	0	0	0	3+
Mid proliferative	0.775		0	0	1+, basal	0	0	4+
Mid proliferative	0.220	180			1+, basal	0	0	1+
Mid proliferative	0.930	147			1+, basal	0	0	2+
Mid proliferative	0.378	404			1+, basal	0	0	2+
Mid proliferative	0.762		0	0	0	0	0	2+
Mid proliferative	3.435	47			0	0	0	1+
Mid proliferative	0.964	138			0	0	0	0
Mid proliferative	0.856	142			0	0	0	1+
Mid proliferative	1.151	123			0	0	0	1+
Mid proliferative	0.122	62			1+, basal, distal	0	0	2+
Mid proliferative	0.442	387			1+, basal	0	0	3+
Late proliferative	2.664	231			1+, basal	0	0	3+
Late proliferative	2.899	308			3+, basal, distal	0	0	4+
Early interval	1.390	527			3+, basal, distal	0	0	4+
Mid interval	0.590	236			2+, basal	0	0	3+
Mid interval	0.354	293			2+, basal, distal	0	0	2+
Mid interval	0.932	66						
Mid interval	1.024	56			1+, basal, distal	0	0	4+
Early differentiative	2.490	93			1+, distal	0	0	4+
Early differentiative	0.550	303					0	1+
Mid differentiative	1.474	924			2+, basal distal	0	0	4+
Late differentiative	1.550		0	0	0	0	0	4+
Late differentiative	0.585	239			0	0	0	4+
Late differentiative	0.200	570			1+, basal	0	0	4+
Late differentiative	1.362	23			0	0	0	3+

P, phenylhydrazine test; R, resorcin-HCl test.

RESULTS

In table 1 are shown the endometrial stage, the weight of the sample, the grams of glycogen per 100 gm. of tissue, the results of the phenyl-hydrazine-HCl reaction and the resorcin-HCl test, the qualitative estimate and the position of the glycogen and mucin in the stained sections.

Proliferative and interval phases. There were 6 specimens in the early proliferative stage which

showed a glycogen content ranging from zero to 0.336 gm. per cent and averaging 0.141 gm. per cent. No glycogen was demonstrated histologically in the glandular or surface epithelium by the oil immersion lens at 900 diameters. The mucin control sections had been made to determine the amount of error due to the reaction of mucin with acid stains and to see if glycogen stained as mucin or if it was possible to stain mucin as glycogen. Also it was desired to determine if glycogen and mucin occupied the same position in the cell and gland lumen. The glycogen was found entirely within the glandular epithelial cell and at its base; the mucin was found in from slight to large amounts in the lumen of the gland and in the uterine cavity.

Zondek has stated (3) that no glycogen has yet been detected in the uterine mucosa of human subjects during the phase of follicular maturation, by means of histochemical methods. In this series there were 12 specimens in the mid-proliferative stage containing glycogen, ranging from zero to 0.404 gm. per cent and averaging 0.110 gm. per cent. The glycogen in this stage was histologically demonstrable in small amounts, or not at all. It usually consisted of fine or coarse granules and was located immediately above or below the nucleus. None was found in the lumen of the gland. Mucin was present in the lumen of the glands.

The progressive increase of the glycogen content is illustrated in a late proliferative specimen containing 0.2314 gm. per cent of glycogen. This tissue, on section, showed a slight amount of basal glycogen and large amounts of mucin in the lumen of the gland.

A late proliferative-early interval specimen contained 0.2087 gm. per cent of glycogen; histologically, large amounts of glycogen appeared in the basal and distal positions of the gland cells. Very large amounts of mucin were found in the lumen of these glands.

One specimen representing the early interval phase contained 0.5274 gm. per cent of glycogen and, on section, large amounts of basal and distal granules of glycogen were demonstrated. Mucin was present in very large amounts.

A decrease of the glycogen content is illustrated in 4 mid-interval specimens of endometrium which contained glycogen ranging from 0.2931 to 0.0561 gm. per cent and averaging 0.1603. Slight to moderate amounts of basal and distal glycogen were demonstrated histologically with moderate to very large amounts of mucin in the lumen of the glands.

Differentiative or secretory phases. Two early differentiative specimens of endometrium contained glycogen ranging from 0.3039 to 0.0930 gm. per cent and averaging 0.1984, which is a higher level than is found in the proliferative phase. Slight amounts of glycogen in the distal portion of the gland epithelium

TABLE 2. CORRELATION OF THE DAY OF THE MENSTRUAL CYCLE WITH THE ENDOMETRIAL STAGE, AND QUANTITIES OF GLYCOGEN OBTAINED BY VARIOUS INVESTIGATORS

Day of Menstrual	Endometrial Stage	Randall & Power				Zondek & Stein				Spyker & Fidler			
		Number of specimens	Glycogen, mg. %			Number of specimens	Glycogen, mg. %			Number of specimens	Glycogen, mg. %		
			Max.	Min.	Average		Max.	Min.	Average		Max.	Min.	Average
9	Early proliferative					2	8	0	4	6	34	0	14
10	Early proliferative					3	25	0	8				
11	Mid proliferative	1	18							12	40	0	12
13	Late proliferative									1	39		
14	Late proliferative	2	26	0	19	1	10			1	23		
15	Early interval	1	113							1	21		
16	Early interval	1	15							1	52		
17	Mid interval	4	126	23	77	1	99			4	29	6	16
18	Mid interval					1	21						
19	Mid interval	1	44			7	47	7	31				
20	Late interval	2	65	36	51	1	7						
21	Late interval	3	69	38	51	2	52	47	49				
22	Early differentiative	3	168	57	100	1	15			2	30	9	20
23	Early differentiative	5	104	53	81	6	49	8	41				
24	Mid differentiative	1	51			3	28	8	28				
25	Mid differentiative	3	102	51	71	4	56	5	43	1	92		
26	Late differentiative	1	37			8	43	16	37				
27	Late differentiative	1	88			4	81	15	66	4	57	0	21
28	Late differentiative	2	72	52	62	1	13						
29	Late differentiative					1	53						
30	Late differentiative Atrophic	1	20			1	31						
49	Late differentiative 'Anovulatory'	1	85			6	16	0	8				

were demonstrated in histologic sections and slight to very large amounts of mucin in the lumen of the glands.

Four late-differentiative samples contained glycogen ranging from zero to a maximum of 0.57 gm. per cent and averaging 0.2081, thus maintaining a higher level than was found in the proliferative phase. The sections showed none to slight amounts of stained glycogen in the glandular epithelium and a moderate amount in the epithelial cells of the surface epithelium. There were large to very large amounts of mucin in the lumen of the glands.

The chemical reactions for carbohydrate, especially glucose, with phenylhydrazine and resorcin hydrochloride, were made on all aliquot samples giving a negative quantity for glucose in the titration with ceric sulphate.

The data in table 2 represents an attempt to correlate the day of the menstrual cycle with the phase of histologic development of the endometrium, by comparing the quantitative amounts of glycogen reported by Randall and Power, by Zondek and Stein, and our data. Randall and Power found the highest percentage of glycogen on *day 22*, the lowest on *day 14*. They obtained consistently high values for specimens from the 17th to 28th days. These were, on an average, well above the estimations on specimens from *days 1* to *17*. Zondek and Stein obtained the highest glycogen percentage in endometrium obtained on *day 17*, the lowest on *days 9* and *10* and in those from patients with anovulatory cycles. The specimens of endometrium in the differentiative stage contained more glycogen than those in the proliferative stage.

In the series of studies in our laboratory the highest glycogen percentage was obtained in the mid-differentiative phase of the endometrial cycle, the lowest in the early proliferative and late differentiative stages. High values for glycogen were obtained in some specimens from the proliferative, interval and differentiative phases of the menstrual cycle, although several samples from each phase showed low values. In this study there was little evidence of the association of the presence of high, medium and low quantities of glycogen in relation to the phases of the cycle as compared with the reports of other workers. The quantities of glycogen in the tissues of the differentiative phase were, on an average, higher than those of the proliferative stage.

COMMENTS

It is noted that graphs of the glycogen content of the endometrium do not coincide particularly with any reported hormone levels influencing the endometrium, but instead, follow these factors by 1 to 3 days. Roughly, the highest percentage of glycogen found by Randall and Power was on *day 15* and the curve remained at a higher level in the differentiative phase than in the proliferative phase. There was a second rise in this graph line on *day 23* and the level following this was still higher than either of the two preceding levels. Zondek and Stein found low glycogen levels in the proliferative phase, with a peak on *day 17* and a sustained level in the differentiative phase which was higher than that in the proliferative stage. Our results show low levels in the proliferative phase with a peak in the mid-proliferative phase, one in the early interval and one in the mid-differentiative phase. The level in the differentiative phase was slightly higher than that of the proliferative phase.

SUMMARY AND CONCLUSIONS

1. From these comparisons the conclusion can be made that proliferative endometrium contains at most only slight amounts of glycogen.

2. In the interval phase the values for glycogen content of the endometrium are increased sharply.

3. There is a postovulatory peak of glycogen content which occurs at about the 15th to 20th day of the cycle.

4. In the differentiative phase, the endometrium contains quantities of glycogen in excess of that in the proliferative stage.

5. The presence of mucin seems to be independent of the hormonal influence. It is relatively less in a stage in which the glycogen metabolism is more normal and is increased in cystic modifications of the endometrium. Mucin was never demonstrated within the cells but only in the lumen of the gland or in the uterine cavity.

6. Glycogen is found chiefly in the epithelial cells of the glands and surface, but it may appear in the gland lumen during the interval and late differentiative phases and also in the uterine cavity.

7. The presence of glycogen in the stroma was rarely evident.

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Effects of Contraphysiologically Administered Diethylstilbestrol on the Menstrual Cycle[1]

[Diethylstilbestrol and Normal Menstrual Cycle]

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Numerous workers have reported that the intermenstrual administration of hormonal estrogens in relatively large doses results in an 'over-riding' of corpus luteum function. Our group, using in this fashion moderate doses of hormonal estrogens in women with normal ovarian function, observed no depressing effects upon corpus luteum function (1).

Since the non-hormonal estrogen, diethylstilbestrol, is available at low cost, its clinical use has been widespread. Unfortunately many of its applications have been and continue to be uncritical. In view of these facts it seemed worth while to investigate the effects of the contra-physiologic use of moderately small doses of diethylstilbestrol in women with normal ovarian function. The present communication deals with this investigation.

METHODS

Thirteen patients in whom episodes of bleeding occurred from a progestational endometrium were chosen for these studies. Their ages ranged from 18 to 32 years and averaged 25.5 years.

Diethylstilbestrol[2] was administered orally in daily amounts ranging from 1 to 6 mg. Treatment was given to 12 patients for 10 days during the first half of the menstrual cycle, from the 5th to the 14th day inclusive. In the case of one patient, who received therapy during 4 menstrual cycles, treatment was begun on the 5th day and ended on the 24th day of each cycle.

Four patients received treatment during a single cycle, 5 patients during 2 consecutive cycles each, 2 patients during 3 consecutive cycles each and 2 patients each received treatment during 4 consecutive menstrual cycles.

The endometrium was sampled for study prior to and during treatment. Similar studies, made during menstrual cycles subsequent to therapy, permitted evaluation of persistent effects of therapy. Endometrial biopsies were obtained within the first 24 hours after the onset of episodes of bleeding. Classification of endometrial responses was made by one of us (E.C.H.).

Data upon the length of the cycle and the duration and amount of bleeding before, during and following therapy were analyzed.

Studies of the urinary excretion of sodium pregnanediol glucuronide in 6 patients were made prior to and during therapy. The method of Venning was employed (2).

All patients had complete medical, gynecologic and endocrine surveys, including determinations of the basal metabolic rate and roentgenograms of the sella turcica.

DATA

The immediate effects of diethylstilbestrol were studied during a total of 32 cycles; the remote effects during another 23 cycles.

Dosage schedules. The daily dosage and the days of therapy, with relation to the menstrual cycle, were distributed as follows.

1 mg., 5th to 14th days inclusive; 10 patients, 26 cycles
1 mg., 5th to 24th days inclusive; 1 patient, 1 cycle

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[1] Part of the expenses of these studies was defrayed by grants to one of us (E.C.H.) from the Research Council of Duke University and from Ayerst, McKenna & Harrison, Ltd., Montreal, Canada.

[2] Estrobene, supplied by Ayerst, McKenna & Harrison, Ltd., Montreal, Canada.

2 mg., 5th to 14th days inclusive; 1 patient, 1 cycle
2 mg., 5th to 24th days inclusive; 1 patient, 1 cycle
3 mg., 5th to 24th days inclusive; 1 patient, 2 cycles
6 mg., 5th to 14th days inclusive; 1 patient, 1 cycle

Effect upon endometrium. The endometrial responses were studied in 15 of the 32 cycles during which therapy was given to 9 of the 13 patients under treatment. In all but one instance, these studies were made after therapy which consisted of 1 mg. of diethylstilbestrol daily from the 5th to the 14th days of the cycle. Two-thirds of the specimens of endometrium were estrogenic in type, while one-third were progestational (table 1).

TABLE 1. SUMMARY OF SERIES OF CONSECUTIVE TREATMENT CYCLES AND OF THE ENDOMETRIAL RESPONSES IN 15 CYCLES SAMPLED

Patient	Series	Consecutive Cycles of Therapy			
		1	2	3	4
1	1	Persistent estrogenic			
2	1	Persistent estrogenic			
3	1	Marked progestational	None		
4	1	Progestational	None		
5	1	None	Persistent estrogenic		
6	1	Persistent estrogenic	None	Persistent estrogenic	
7	1	Persistent estrogenic	Persistent estrogenic	Persistent estrogenic	
8	1	Progestational	None		
	2	Persistent estrogenic[1]			
9	1	None			
	2	None			
	3	None	Progestational	Persistent estrogenic	Marked progestational
10	1	None			
	2	None			
11	1	None			
12	1	None	None		
13	1	None	None	None	None

[1] Following 2 mg. of diethylstilbestrol daily from 5th to 14th days inclusive.

Endometrial studies were made on 3 patients during a total of 13 cycles subsequent to the cessation of therapy. Twenty per cent of the specimens were estrogenic in character, while 80 per cent were progestational in type (table 2). These follow-up studies were made on patients who had been previously treated during 2 to 4 consecutive cycles.

Effects upon length of the cycle. There was consistent shortening of the cycles in 5 patients, the average length being reduced from 29.6 days prior to therapy, to 20.3 days during treatment. The cycles of 2 patients were consistently lengthened during therapy, the average being increased from 25.4 days prior to therapy to 38.2 days during treatment. Alterations in the length of the cycles of 5 patients were not constant in any one direction. The average length of the cycle of these patients prior to therapy was 28 days and during treatment was 27.6 days. There was no significant change in the length of the cycles of one patient during therapy.

Subsequent to the cessation of diethylstilbestrol therapy 3 patients, who had had consistently shortened cycles during therapy, were investigated for 13 cycles. The average length of these was 29.1 days. The average length before and during treatment had been 26.8 and 21.2 days, respectively. Nine cycles of 4 patients, who had had varying alterations in the length of cycles during therapy, averaged 25.6 days in length following cessation of treatment. Prior to and during treatment the average length was 27.9 and 28.7 days, respectively. Variations in the length of the cycles, as well as other pertinent data, of 2 of these patients, are given in figures 1 and 2.

Only one episode of uterine bleeding occurred concomitantly with therapy. In this instance, bleeding began on the 3rd day of treatment and terminated with the course of therapy 8 days later. Estrogen withdrawal bleeding followed after 5 days.

TABLE 2. SUMMARY OF SERIES OF CONSECUTIVE CYCLES INVESTIGATED FOLLOWING THERAPY AND OF THE ENDOMETRIAL FINDINGS IN 11 CYCLES SAMPLED

Patient	Following Series of Treatment	Consecutive Cycles Following Therapy			
		1	2	3	4
6	1	None	None	None	None
7	1	Moderate progestational	Hyperestrogenic	None	Moderate progestational
8	1	None			
9	1	Progestational	None	Progestational	
	2	Progestational	Persistent estrogenic		
	3	Moderate progestational			
10	1	Progestational			
	2	None	Progestational		
12	1	None			
13	1	None	None	None	

Effect upon duration and amount of uterine bleeding. There was a tendency for changes in the duration of bleeding during therapy to parallel the alteration in the length of the cycle. Those patients who had con-

sistently shortened cycles experienced shorter episodes of bleeding, while those who had lengthened cycles had notably longer bleeding phases. Those patients in whom alterations in the length of the cycle were variable experienced no significant changes in the duration of bleeding. These tendencies disappear, however, when averages of the duration of bleeding for the whole group before, during and after therapy are considered. These averages were 5.8 days, 5.0 days and 6.8 days, respectively.

It was observed that the episodes of bleeding which followed the first cycle after cessation of therapy generally were longer than the average duration prior to treatment. In subsequent cycles, however, bleeding phases of normal length often recurred.

The influence of therapy upon the amount of uterine bleeding was of the same order as that upon the duration of bleeding. The patients who experienced shortened cycles as a result of therapy reported a decrease in the number of sanitary pads required. An increase in the number of pads required was reported by those patients who had lengthened cycles. No significant findings were encountered in patients who experienced no characteristic alterations of menstrual flow. The average number of well-saturated pads

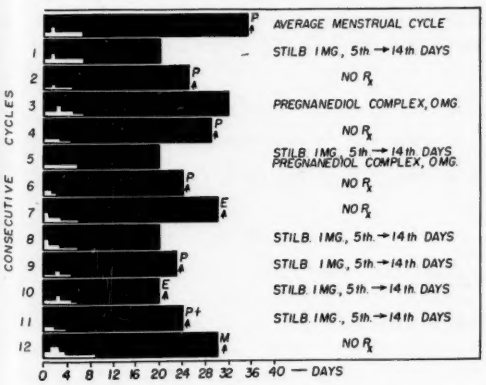
AVERAGE MENSTRUAL CYCLE
STILB. 1 MG., 5th. → 14th. DAYS
NO Rx
PREGNANEDIOL COMPLEX, 0 MG.
NO Rx
STILB. 1 MG., 5th. → 14th. DAYS
PREGNANEDIOL COMPLEX, 0 MG.
NO Rx
NO Rx
STILB. 1 MG., 5th. → 14th. DAYS
STILB. 1 MG., 5th. → 14th. DAYS
STILB. 1 MG., 5th. → 14th. DAYS
STILB. 1 MG., 5th. → 14th. DAYS
NO Rx
CONSECUTIVE CYCLES
0 4 8 12 16 20 24 28 32 36 40 — DAYS

FIG. 1. EFFECTS OF DIETHYLSTILBESTROL (Stilb.) on duration of bleeding cycles, endometrial responses (P and P+, progestational; E, estrogenic) and pregnanediol excretion of *patient 9*. Episodes of bleeding are represented for each cycle at the left of the graph.

used by the group as a whole prior to, during and after therapy were 13, 10 and 13, respectively.

Effects upon withdrawal bleeding time. The criterion employed for the definition of withdrawal bleeding was the occurrence of an episode of bleeding within a few days after cessation of therapy and considerably in advance of the expected date of bleeding. In 14 cycles of 7 treated patients the withdrawal bleeding time averaged 6 days. The range was from 2 to 8 days. The length of these cycles averaged 19.5 days. In the case of the only patient in whom therapy lasted from the 5th to the 24th day of the cycle, the time between cessation of therapy and the onset of bleeding averaged 2.8 days. The average length of the cycle of this patient prior to treatment was 25.4 days.

Effect upon urinary excretion of sodium pregnanediol glucuronide. Determinations of the pregnanediol-complex levels were made on the urine of 6 patients during a total of 6 cycles prior to therapy, and during

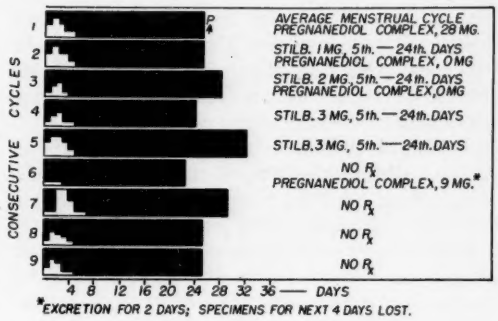
AVERAGE MENSTRUAL CYCLE PREGNANEDIOL COMPLEX, 28 MG.
STILB. 1 MG, 5th. — 24th. DAYS PREGNANEDIOL COMPLEX, 0 MG
STILB. 2 MG, 5th. — 24th. DAYS PREGNANEDIOL COMPLEX, 0 MG
STILB. 3 MG, 5th. — 24th. DAYS
STILB. 3 MG, 5th. — 24th. DAYS
NO Rx PREGNANEDIOL COMPLEX, 9 MG.*
NO Rx
NO Rx
NO Rx
CONSECUTIVE CYCLES
4 8 12 16 20 24 28 32 36 — DAYS
*EXCRETION FOR 2 DAYS; SPECIMENS FOR NEXT 4 DAYS LOST.

FIG. 2. EFFECTS OF DIETHYLSTILBESTROL (Stilb.) on duration of bleeding cycles and pregnanediol excretion of *patient 13*. Episodes of bleeding are represented for each cycle at the left of the graph.

a total of 7 cycles in these patients during treatment. Only 2 patients excreted the complex prior to therapy; 28 and 31 mg., respectively, were recovered. No pregnanediol complex was recovered in any of the patients during treatment. Endometrial studies were made at the onset of bleeding in 3 cycles of 3 of these patients during treatment. The endometria were estrogenic in nature.

The number of determinations of the pregnanediol complex averaged 13 per patient prior to therapy, and 19 per patient during treatment.

Untoward effects. No significant untoward effects of therapy were observed or reported by the patients.

DISCUSSION

The contraphysiologic employment of moderately small doses of the non-hormonal estrogen, diethystilbestrol, in women with normal ovarian function produced definite effects upon the menstrual cycle. These effects were manifested in the various elements characteristic of the menstrual cycle, i.e., the status of the endometrium at the onset of bleeding, the length of the cycle and duration and character of the flowing.

The occurrence of depressions of corpus luteum function in a number of instances was indicated by the preponderance (67%) of specimens of estrogenic endometria over progestational ones (33%) during therapy. This effect often occurred during the first cycles of treatment. Of 8 endometrial samples taken

at this time, 5 were estrogenic and 3 were progestational in nature.

Diethylstilbestrol therapy was associated with disturbances in the cyclic nature of bleeding in all but one patient. These alterations in the amount of bleeding were not directly proportional to alterations in duration of bleeding, but represented an actual increase or decrease of the flow.

Variations in endometrial response and in alteration of the bleeding cycles of patients, and, in several instances, of the same individual, on the same dosage, are worthy of note. These differences may be explained on the basis of individual ovarian capacity and the varying tolerance of these patients to an exogenous synthetic non-hormonal estrogen.

It is apparent from the data presented that the effects of diethylstilbestrol on the menstrual cycle, which were observed during treatment, are not cumulative. No instances of prolonged persistent depression of ovarian function were encountered. Progestational endometrium was found in each of 5 instances wherein endometrial samples were obtained at the end of the first cycle which occurred subsequent to the cessation of therapy, despite the fact that some of these patients had received therapy during 2 to 4 antecedent cycles. The occurrence of progestational endometrium in 80 per cent of the specimens obtained during cycles following therapy, the recurrence of cyclic bleeding and the return of flow to one of normal duration and amount following cessation of therapy, are additional evidence that, in the dosages and manner of administration employed, diethylstilbestrol has no lasting undesirable effects. These findings, however, do not warrant any statement with regard to the ultimate results that follow protracted therapy with larger doses of diethylstilbestrol.

SUMMARY

Moderately small doses of diethylstilbestrol were used contraphysiologically in 13 women who had normal ovarian function. Depression of corpus luteum function during therapy was indicated by bleeding from an estrogenic endometrium in two-thirds of the cycles during which the endometrium was sampled. The failure to recover sodium pregnanediol glucuronide from the urine of 6 patients during therapy was taken as further evidence for depression of corpus luteum function.

Marked alterations in the menstrual cycle occurred with regard to length of the cycle and to duration and amount of bleeding.

The effects of diethylstilbestrol apparently are not cumulative when it is used in therapeutic schedules comparable to those reported. No prolonged, undesirable effects were noted. Progestational endometrium was encountered in all biopsies which were secured at the end of the first cycle which followed cessation of therapy. These findings do not warrant any statement regarding results that might follow the prolonged use of diethylstilbestrol in larger doses.

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Effects of Desoxycorticosterone Acetate on 17-Ketosteroid and Pregnanediol Excretions[1]

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In an earlier report, by members of our group, which considered the progesterone-like effect of desoxycorticosterone acetate administered intramuscularly to women, it was observed that no evidence existed that desoxycorticosterone acetate was metabolized into androgenic substances (1). More recently, additional data have been gathered which are relative to this point. Determinations for 17-ketosteroids were made on the urine of 2 patients with Addison's disease who were being treated with desoxycorticosterone acetate.[2] The results of these led to further studies of the administration of this substance to normal individuals. The present communication deals with these studies.

Methods

The individuals studied were divided into 3 groups as follows: *group 1*, patients with Addison's disease; *group 2*, women with intercurrent ovarian failure associated with the absence of uterine bleeding; *group 3*, normal individuals.

Group 1 consisted of 2 patients, a woman aged 32 years and a man aged 39 years, who were hospitalized for an evaluation of presumed Addison's disease. Studies of daily 24-hour urine specimens were made on both patients during hospitalization. These were continued on the woman after her discharge from the hospital and were resumed upon her return for additional therapy. Determinations of urinary 17-ketosteroids were made in the case of both patients prior to and during therapy. The urinary excretion of sodium pregnanediol glucuronide was studied only in the woman and after initiation of treatment.

Group 2 was comprised of 5 women who had intercurrent ovarian failure which was associated with the absence of uterine bleeding for periods ranging from 3 to 9 months. The average age of these patients was 25 years. Urinary levels of 17-ketosteroids and of the pregnanediol complex were determined prior to and during therapy. The therapeutic schedule employed was essentially the following. Estrone (10,000 I.U.) or estradiol benzoate (2000 R.U.) was given intramuscularly daily for 14 consecutive days; desoxycorticosterone acetate (5 mg.) and either estrone (10,000 I.U.) or estriol glucuronide (1800 oral units) was given daily the next 14 days (therapy being discontinued, however, if bleeding began). One patient received two cycles of this therapy. The total dosage of desoxycorticosterone acetate ranged from 35 mg. to 60 mg. per cycle with an average of 47.5 mg.

Group 3 consisted of 5 healthy individuals who volunteered for this investigation. In the group were 3 men whose ages averaged 26 years and 2 women whose average age was 26 years. The women each received desoxycorticosterone acetate intramuscularly, 5 mg. daily for 5 days, beginning on the 12th day of the menstrual cycle. The men each received intramuscularly 10 mg. of desoxycorticosterone acetate daily for 5 days. Two of the men each had 2 courses of treatment. Consecutive 24-hour-urine specimens were collected, beginning 4 days prior to initiation of therapy and ending from 4 to 11 days following the last injection. Levels of 17-ketosteroids were established on all individuals. The pregnanediol-complex excretion was studied only in the males. The average daily titers of 17-ketosteroids were established as follows: *a*), prior to treatment; *b*), during

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[1] Part of the expenses of these studies was defrayed by grants to one of us (E.C.H.) from the Research Council of Duke University and from Schering Corporation, Bloomfield, N. J.

* Deceased, April 10, 1942.

[2] Cortate, supplied by Schering Corporation, Bloomfield, N. J.

treatment and c), following treatment. The term 'during treatment' was defined to include the 5 days of treatment and the first 2 days following cessation of therapy.

The estimation of 17-ketosteroids was made colorimetrically by the method of Oesting (2, 3),

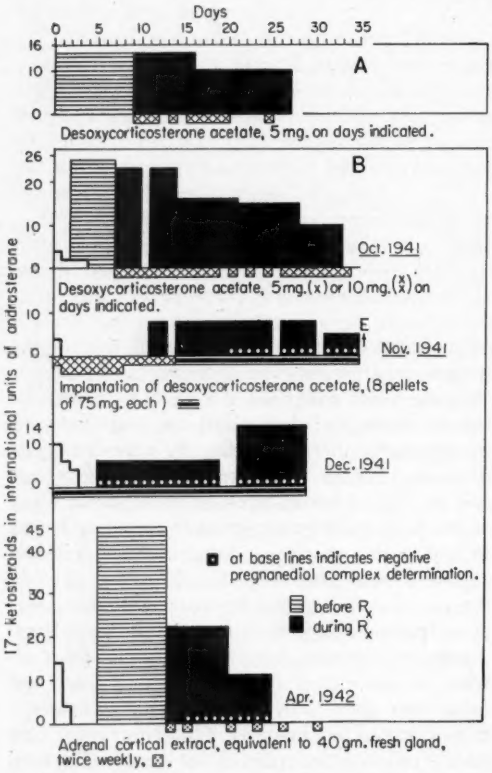
Days
0 5 10 15 20 25 30 35
A
Desoxycorticosterone acetate, 5 mg. on days indicated.
B
Oct. 1941
Desoxycorticosterone acetate, 5 mg.(x) or 10 mg.(x/x) on days indicated.
E
Nov. 1941
Implantation of desoxycorticosterone acetate, (8 pellets of 75 mg. each)
Dec. 1941
at base lines indicates negative pregnanediol complex determination.
before Rx
during Rx
Apr. 1942
Adrenal cortical extract, equivalent to 40 gm. fresh gland, twice weekly.
17-ketosteroids in international units of androsterone

FIG. 1, A. *Patient F. N.* ♂ ADDISON'S DISEASE. Levels of urinary 17-ketosteroids associated with desoxycorticosterone therapy. B. *Patient M. T.* ♀ ADDISON'S DISEASE. Levels of urinary 17-ketosteroids and sodium pregnanediol glucuronide associated with therapy consisting of desoxycorticosterone acetate and adrenal cortical extract. Episodes of uterine bleeding are represented at the beginning of each cycle by outlined blocks. *E* signifies persistent estrogenic endometrium judged by endometrial biopsy.

after urinary extraction by the method of Cuyler and Baptist (4). Determinations of sodium pregnanediol glucuronide were made by Venning's method (5).

DATA

Patients with Addison's disease. The data on these patients are presented in the following short summaries and in figure 1.

Patient F. N., a 39-year-old white married male was referred to the Endocrine Division for an evaluation of symptoms and consideration of therapy. Response to therapy with desoxycorticosterone acetate was unfavorable. The patient was discharged and placed on a high sodium chloride intake. Figure 1, A, relates details of treatment with desoxycorticosterone acetate and daily excretion levels of 17-ketosteroids averaged by weeks.

Patient M. T., a 32-year-old, white housewife, para 3, 0, 3, was referred to the Endocrine Division for an evaluation of symptoms and recommendations as to therapy. Trials of treatment with an increased salt intake and varying doses of desoxycorticosterone acetate were made. Eight pellets of 75 mg. each of this substance were implanted subcutaneously in the right subscapular region. Progress in the hospital after implantation of pellets was satisfactory. For a few weeks following discharge, the patient showed evidences of over-treatment. Five months after initial treatment, further therapy was required. This consisted of intramuscular administration of adrenal cortical extract.[3] Details of therapy and related urinary levels of 17-ketosteroids and the pregnanediol complex are shown in figure 1, B. The daily 17-ketosteroid excretion levels are reported in terms of weekly averages. This patient had had infrequent uterine bleeding prior to treatment. Under therapy, periodic bleeding was re-established.

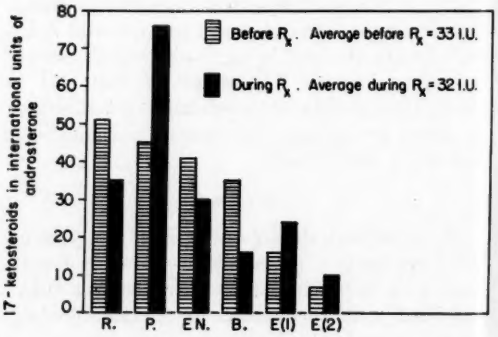
Before Rx. Average before Rx = 33 I.U.
During Rx. Average during Rx = 32 I.U.
17-ketosteroids in international units of androsterone
R. P. EN. B. E(1) E(2)

FIG. 2. LEVELS OF URINARY 17-KETOSTEROIDS before and during desoxycorticosterone acetate therapy in 5 women with intercurrent ovarian failure. *Patient E* had 2 series of study.

Patients with intercurrent ovarian failure. None of these 5 patients excreted sodium pregnanediol glucuronide prior to treatment. During therapy, the pregnanediol complex was recovered from the urine of 3 patients in total amounts of 3, 6 and 9 mg., respectively. Uterine bleeding followed treatment in one of these 3 patients. Endometrial studies in 2 of these 3 patients showed persistent estrogenic endometria. The averaged daily excretion levels of urinary

[3] The adrenal cortical extract was prepared by The Upjohn Co., of Kalamazoo, Mich.

17-ketosteroids prior to and during therapy are presented in figure 2.

Normal individuals. No pregnanediol complex was recovered from the urine of the 3 males studied. The averaged daily levels of 17-ketosteroid excretion before, during and following treatment are presented in figure 3. Therapy had no effect upon the regularity of uterine bleeding in the two female patients.

DISCUSSION

17-Ketosteroid levels. A depression of urinary 17-ketosteroid levels followed institution of therapy with desoxycorticosterone acetate in each of the two patients with Addison's disease. In the female, depressed values continued during 3 bleeding cycles. This finding is not in agreement with those of the workers (6) who found a very slight increase in 17-ketosteroid values during administration of desoxycorticosterone acetate of comparable dosage to women with Addison's disease. This difference may be accounted for in the status of the patients, or possibly in the number of determinations made in establishing levels before and during therapy.

Our two patients were not in a particularly grave state of adrenal cortical insufficiency. This is reflected in the fact that one patient (*F. N.*) could be maintained on increased salt intake alone and that, in the replacement therapy in the second patient the maintenance dosage was finally found to be rather small. The pretreatment levels of urinary 17-ketosteroids in these patients were of the same order as reported by others in association with Addison's disease (6, 7).

The depression in 17-ketosteroid levels in the case of the female, figure 1, B, occurred during intramuscular administration of desoxycorticosterone acetate, persisted for a time during therapy by pellet implantation and was observed also after the administration intramuscularly of an adrenal extract, in amounts equivalent to 40 gm. of fresh tissue, twice weekly. This amount (40 gm.) corresponds roughly to 0.15 mg. of desoxycorticosterone acetate (8, 9). The increased 17-ketosteroid level of the female patient upon her second hospital visit may be related to the exhaustion of the implanted pellets.

It is apparent from figures 2 and 3 that no consistent alterations of 17-ketosteroid levels follow administration of desoxycorticosterone acetate to patients with intercurrent ovarian failure or to normal individuals. In the cases of these groups of individuals, the data do not offer conclusive evidence of depressing effects upon the adrenal cortex. Since desoxycorticosterone acetate has been shown to have an estrogenic action in woman (10) and since our group found decreased 17-ketosteroid levels in women during estrogenic therapy (11), it was expected that decreased levels might follow administration of desoxycorticosterone acetate. However, the results were equivocal: in the two normal women there was virtually no alteration of 17-ketosteroid levels during therapy, while in the case of women with intercurrent ovarian failure, 3 patients had decreased levels and 2 patients had increased levels during treatment.

It cannot be concluded from the data presented that desoxycorticosterone acetate, after intramuscular administration or pellet implantation, is altered to

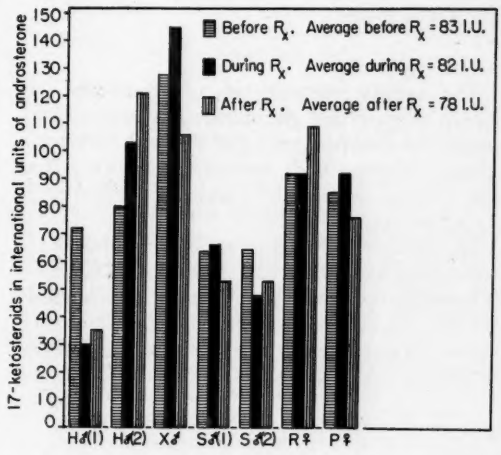

FIG. 3. LEVELS OF URINARY 17-KETOSTEROIDS before, during and after desoxycorticosterone acetate therapy in 5 normal individuals, 3 men and 2 women. Two of the men (*H* and *S*) had 2 series of study.

products which are recoverable by our procedure for extracting urinary 17-ketosteroids.

With regard to the alteration in 17-ketosteroid level during therapy with desoxycorticosterone acetate, no constant change was observed in individuals who had normal adrenal function. On the other hand, evidence is presented (fig. 1, B) that in Addison's disease this level varies inversely with dosage and extent of therapy. This correlation may prove to be an indicator of pellet exhaustion before clinical symptoms and signs re-appear.

Excretion of sodium pregnanediol glucuronide. No pregnanediol complex was recovered from the urine of the female patient with Addison's disease during treatment with desoxycorticosterone acetate or with adrenal cortical extract. Only small amounts of the complex were recovered during therapy from the urine of the patients with intercurrent ovarian failure. The normal males excreted no urinary pregnanediol complex during therapy. We do not regard this last finding as conflicting necessarily with a previous report by our group (12) which described

the recovery of sodium pregnanediol glucuronide from the urine of a healthy male during the administration of desoxycorticosterone acetate. Marked variations exist in the ability of different males to metabolize progesterone administered intramuscularly (13) and to excrete ingested sodium pregnanediol glucuronide (14). However, the difference between the results on the males in the present study and the results reported previously may be one of age. The ages of the normal males in this study ranged from 21 to 31 years. The age of the male reported previously (12) was 39 years.

SUMMARY

The urinary excretion of 17-ketosteroids and sodium pregnanediol glucuronide has been studied during the treatment of 2 patients with Addison's disease, 5 women with intercurrent ovarian failure and 5 normal individuals (3 males, 2 females) with desoxycorticosterone acetate.

No constant alterations in the urinary levels of 17-ketosteroids were observed during the administration of desoxycorticosterone acetate to normal individuals of either sex, or to women with intercurrent ovarian failure. Therapy with desoxycorticosterone acetate or adrenal cortical extract in Addison's disease was associated with a decrease in 17-ketosteroid levels.

No evidence was encountered that any of the desoxycorticosterone acetate given was metabolized into sodium pregnanediol glucuronide.

The authors wish to express their appreciation to those individuals who volunteered their services for these studies.

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Progesterone Therapy and Progestin Metabolism in Abortion[1]

[Progesterone and Abortion]

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The Council on Pharmacy and Chemistry of the American Medical Association recently stated: 'It is indeed difficult to conclude from the available data whether or not progesterone or active corpus luteum extracts are of value in the treatment of habitual and threatened abortion' (1). The accurate evaluation of therapy, of necessity, must remain difficult until we have a better understanding of the etiologic factors in abortion.

Diagnosis of threatened abortion has been rendered uncertain by the fact that biologically active progestin is identified in human tissues and fluids in only small quantities by the present methods of bioassay. Some of the more recent and more sensitive of these methods have not been applied to clinical studies.

Venning's (2) method for the determination of pregnanediol, an excretion product of progestin metabolism, aroused much enthusiasm. It was hoped that, at last, there was a diagnostic implement by which significant alterations in intrinsic progestin levels might be determined. The matter of raising the lower of these levels was deemed to be practical since crystalline progesterone was available.

Five years now have elapsed since Venning's method was described. During the last four years in our laboratory a total of 7142 twenty-four-hour-urine specimens of 235 women has been examined for pregnanediol. A total of 788 twenty-four-hour urine specimens has been studied on 14 obstetric patients.

This communication evaluates progestin therapy with reference to its general effectiveness in warding off abortion or miscarriage and to its relationship to levels of corpus luteum and chorio-placental function in pregnancy.

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[1] Part of the expenses of these studies was defrayed by grants to one of us (E.C.H.) from the Research Council of Duke Hospital, from Schering Corp., Bloomfield, N. J., and from Ayerst, McKenna and Harrison, Montreal, Canada.

METHODS

Each patient included in this report received complete gynecologic and endocrine surveys which comprised thorough general physical examinations, anthropometric measurements, basal metabolic determinations, roentgenograms of the sella turcica, and other special examinations when these were deemed indicated.

The diagnosis of pregnancy was substantiated by hormone tests when the duration of pregnancy prevented positive diagnosis by pelvic examinations.

In some of these cases consecutive 24-hour specimens of urine were collected for sodium pregnanediol glucuronide determinations. The Venning method was followed. Our results are reported as daily excretions, averaged by weeks, and in terms of milligrams of sodium pregnanediol glucuronide.

THERAPEUTIC REGIMEN

No one regime has been followed in our therapy to prevent abortion. The common element in all regimen has been progestin or crystalline progesterone.[2] The weekly dosage ranged from 3 to 140 mg.

We have employed also many of the time-honored methods, including bed rest when symptoms were present, decreased activity at all times and abstinence from intercourse.

Those patients with histories of recurrent abortions were treated as soon as the diagnosis of pregnancy was made or when the patients first came under our care. The amount of progesterone employed varied from 10 mg. daily to 5 mg. twice weekly. Five patients received anhydrohydroxyprogesterone[3] orally in daily amounts ranging from 20 to 60 mg. As a rule,

[2] Progestin was supplied by Eli Lilly & Company, Indianapolis, Ind.; progesterone was supplied by Schering Corp., Bloomfield. N. J., and by Ciba Pharmaceutical Products, Inc., Summit, N. J.

[3] Anhydrohydroxyprogesterone (Pranone), supplied by Schering Corp., Bloomfield, N. J.

TABLE 1. PERTINENT CLINICAL DATA OF PATIENTS WITH HISTORIES OF RECURRENT ABORTIONS

Case No.	Parity	Treatment Formula[1]	Week Progesterone Therapy Begun	Week Symptoms Occurred	Week Progesterone Therapy Discontinued	Week Pregnancy Terminated
1	3-3-0	Progesterone and thyroid	16		36	40
2	4-4-0	Progesterone and thyroid	5		33	33
3	2-2-0	Progest.+ch. gonad.+est. gluc.+thyr.+anhydox-prog.	6		33	40
4	8-7-0	Anhydox-prog.+thyr.	18		41	41
5	5-4-1	Progest.+ch. gonad.+est. gluc.	6		R continues	Undelivered; patient in 34th week
6	3-3-0	Progest.+ch. gonad.+est. gluc.+thyr.	5		R continues	Undelivered; patient in 33rd week
7	2-2-0	Progest.+est. gluc.+thyr.	5		R continues	Undelivered; patient in 32nd week
8	5-5-0	Anhydox-prog.+est. gluc.+thyr.	20		26	Undelivered; patient in 32nd week
9	10-10-0	Anhydox-prog.+thyr.	8	30	30	30 (neonatal death)
10	6-5-1	Progest.+ch. gonad.+est. gluc.	11	29	29	29 (stillbirth)
11	4-4-0	Progest.+est. gluc.+thyr.	10	13	13	13
12	3-3-0	Progest.+ch. gonad.+est. gluc.+thyr.	6	24	27	25
13	3-3-0	Progest.+ch. gonad.	6	31	31	31
14	8-8-0	Progest.+ch. gonad.+est. gluc.	15	19	19	19
15	3-3-0	Progest.+ch. gonad.	5	12	12	12
16	4-4-0	Anhydox-progest.+est. gluc.+thyr.	12	15	15	15

[1] Treatment Formula: Progest., progesterone; Anhydox-prog., anhydrohydroxyprogesterone; Est. gluc., estriol glucuronide; Ch. gonad., chorionic gonadotropin; Thyr., thyroid substance.

TABLE 2. PERTINENT CLINICAL DATA OF PATIENTS WITH HISTORIES OF THREATENING ABORTION

Case No.	Parity	Treatment Formula[1]	Week Progesterone Therapy Begun	Week Symptoms Occurred	Week Progesterone Therapy Discontinued	Week Pregnancy Terminated
17	1-1-0	Progest.+ch. gonad.+est. gluc.	7	7	36	40
18	2-0-2	Progest.+est. gluc.+anhydox-prog.	23	23	28	38
19	0-0-0	Anhydox-prog.+thyr.	11	11	33	38
20	1-0-1	Progest.+ch. gonad.+est. gluc.+thyr.	19	17	28	40
21	2-0-2	Progest.+anhydox-prog.+thyr.	23	18	30	41
22	2-2-0	Progest.+est. gluc.+thyr.	25	23	38	41
23	0-0-0	Progest.+est. gluc.+anhydox-prog.	17	16	22	38
24	0-0-0	Progest.+est. gluc.	23	23	24	31
25	0-0-0	Progest.+ch. gonad.+est. gluc.+anhydox-prog.+thyr.	13	13	37	40
26	0-0-0	Anhydox-prog.+thyr.	15	14	23	39
27	0-0-0	Progest.+ch. gonad.+est. gluc.	13	12	27	35
28	3-2-0	Progest.+est. gluc.	20	20	25	38
29	0-0-0	Progest.+thyr.	17	17	17	40
30	1-1-0	Progest.+est. gluc.	11	10	R continues	Undelivered; patient in 33rd week
31	0-0-0	Progest.+ch. gonad.+estrad. benz.+anhydox-prog.+thyr.	13	7	R continues	Undelivered; patient in 20th week
32	0-0-0	Progest.+est. gluc.+anhydox-prog.+thyr.	19	19	R continues	Undelivered; patient in 34th week
33	1-0-1	Anhydox-prog.+est. gluc.+thyr.	8	8	R continues	Undelivered; patient in 26th week
34	1-1-0	Progest.+ch. gonad.+est. gluc.+thyr.	9	9	12	12
35	1-1-0	Progest.+ch. gonad.+est. gluc.	6	5	13	13
36	5-5-0	Progest.+thyr.	8	7	13	13
37	0-0-0	Progest.+ch. gonad.+est. gluc.	11	8	14	Missed abortion
38	4-3-1	Progest.+est. gluc.	15	15	18	18
39	2-1-1	Progest.+ch. gonad.+est. gluc.	9	8	12	12
40	0-0-0	Progest.+ch. gonad.+est. gluc.	11	11	12	12
41	0-0-0	Progest.+ch. gonad.+est. gluc.	12	12	13	13
42	1-1-0	Progest.+est. gluc.	14	5	17	17
43	1-0-1	Progest.+ch. gonad.+est. gluc.	7	7	8	8
44	0-0-0	Progest.+est. gluc.	5	5	6	6
45	2-2-0	Progesterone	7	7	8	8
46	5-2-3	Progesterone	10	7	10	23

[1] See footnote, table 1; Estrad. benz., estradiol benzoate.

TABLE 3. PERTINENT CLINICAL DATA OF PATIENTS INCLUDED IN THE PROGNOSTICATED ABORTION GROUP

Case No.	Parity	Treatment Formula[1]	Week Progesterone Therapy Begun	Week Symptoms Occurred	Week Progesterone Therapy Discontinued	Week Pregnancy Terminated
47	0-0-0	Progest.+ch. gonad.+est. gluc.+thyr.	7	9 through 11	36	40
48	0-0-0	Progesterone	7		20	40
49	1-1-0	Progest.+est. gluc.	10		33	39
50	0-0-0	Anhydox-prog.+est. gluc.+thyr.	12		32	39
51	0-0-0	Progest.+ch. gonad.+est. gluc.+thyr.	7		34	40
52	0-0-0	Progest.+ch. gonad.+est. gluc.+thyr.	7		R continues	Undelivered; patient in 30th week
53	0-0-0	Progest.+est. gluc.+thyr.	7	7	8	8
54	1-1-0	Progest.+corp. lut. ext.+thyr.	10	17	17	17

[1] See footnote, table 1; Corp. lut. ext., corpus luteum extract.

dosage was reduced as pregnancy progressed. Usually therapy was discontinued about the 33rd to the 36th week. In the majority of instances estriol glucuronide[4] chorionic gonadotropin[5] in amounts ranging from 300 to 600 I.U. was given every day or every other day until the 16th to 18th week. When it seemed to be

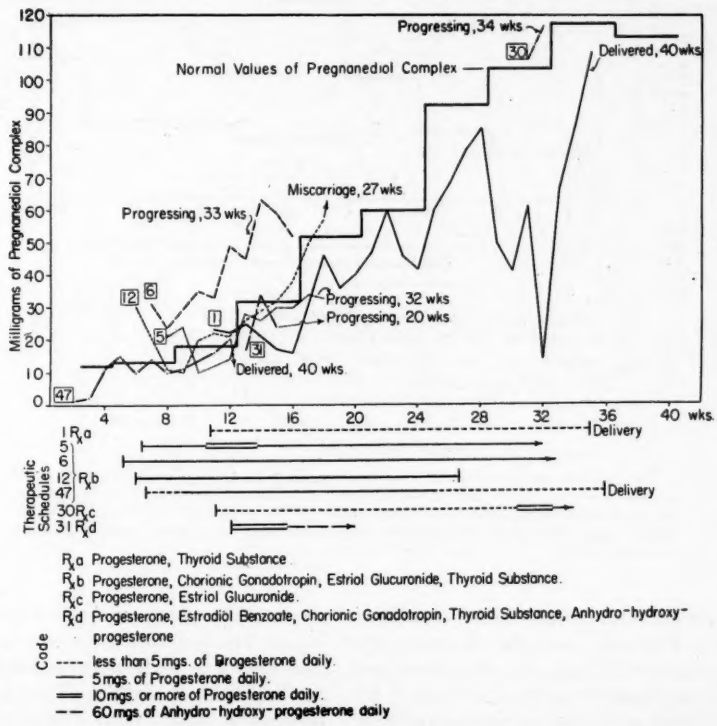

FIG. 1. URINARY EXCRETION OF PREGNANEDIOL-COMPLEX, therapy and clinical course of *patients 1, 5, 6, 12, 30, 31, 47*. The pregnancies of 6 of these 7 progressed normally or went to term. The values for pregnanediol-complex are expressed as daily values in mg. averaged by weeks and in terms of sodium pregnanediol glucuronide. The excretion values in these patients compare favorably with the average normal for other workers (4–9), indicated by heavy lined graph.

was given orally in daily doses ranging from 480 to 960 day-oral units. In about one-half of the patients, indicated, thyroid substance was given to full clinical tolerance during the course of pregnancy.

[4] Estriol glucuronide (Emmenin), supplied by Ayerst, McKenna & Harrison, Montreal, Canada.

[5] APL, supplied by Ayerst, McKenna & Harrison, Montreal, Canada.

The patients with threatening abortion were hospitalized. Essentially the same type of therapy and dosage was used as in the patients with histories of recurrent abortion. However, there was a tendency to use larger doses of progesterone (10 to 20 mg.) during the time acute symptoms were present. Nine of these patients received, eventually, anhydrohydroxyprogesterone.

In the patients of the prognosticated abortion group the pre-pregnancy therapy had consisted of either thyroid substance (2 patients) or cyclic gonadotropic therapy (6 patients). The latter has been described previously by us (3). The therapy for prevention of abortion in these patients was essentially the same as that used in the other groups. Treatment was started as soon as the diagnosis of pregnancy was made. One patient was given oral anhydrohydroxyprogesterone, in place of progesterone, in daily doses of from 20 to 40 mg.

The progesterone therapy of those patients included in the 'pregnanediol group' is presented graphically. As this is a composite group, including members of each of the three diagnostic groups, a fair cross section of results of our progesterone therapy is available.

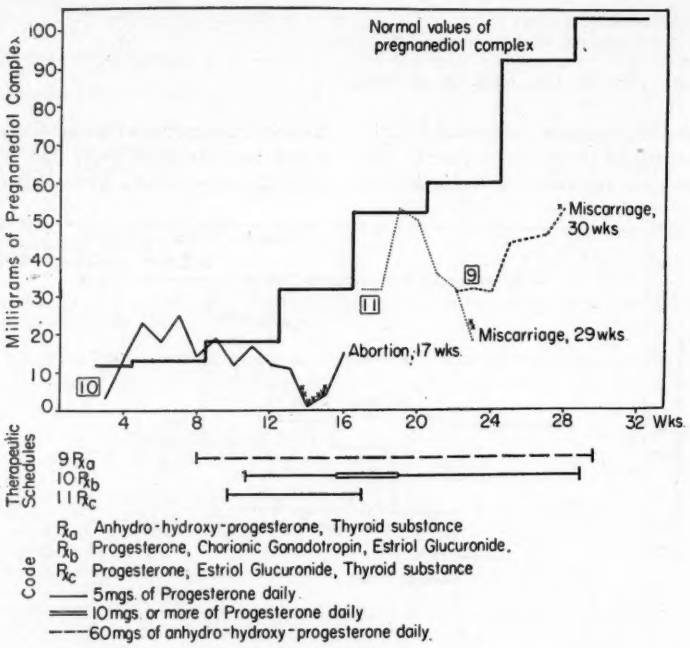

FIG. 2. URINARY EXCRETION OF PREGNANEDIOL-COMPLEX, therapy and clinical course of *patients 9, 10, 11*. All of these patients aborted or miscarried. See figure 1 for explanation of pregnanediol-complex values. These values for the 3 patients were initially within normal range but became depressed with daily zero values immediately prior to abortion or miscarriage.

CLINICAL DATA

Tables 1 to 3 present the pertinent clinical data of the 54 patients studied. These patients have been grouped as follows. *a*), *Recurrent abortion*. This included 16 patients who had histories of 2 or more previous spontaneous abortions. *b*), *Threatening abortion*. This group consisted of 30 patients who had vaginal bleeding during the first 28 weeks of pregnancy, with or without the accompaniment of pain. *c*), *Prognosticated abortion*. This group comprised 8 patients who had been diagnosed as having had ovarian failure and whose pregnancies resulted from therapeutic measures predicated upon this diagnosis.

The sodium pregnanediol glucuronide excretion in the 14 patients studied by Venning's method are given in figures 1 to 3. Eight of these patients are included in the recurrent abortion group, 5 in the threatening abortion group and 1 in the group of prognosticated abortion.

DISCUSSION

The literature on progesterone therapy in recurrent and threatening abortion has been reviewed recently by Kotz, Parker and Kaufman (10). In this report there was 79 per cent success in a collected group of 273 patients with histories of recurrent abortions, and in a total of 69 patients with histories of threatening abortion, therapy was successful in 81 per cent. Kotz et al. reported treatment of 42 patients, with histories of recurrent abortion or ovarian sterlity, with success in 88 per cent of the cases. In their threatening abortion group of 184 patients, 139 were treated with progesterone and 45 received no progesterone. Forty-six per cent of the treated patients went to term and 49 per cent of those who received no progesterone went to term.

Our results are poorer than most of those reported in the literature. Our successes were 57 per cent in the threatening abortion group, 50 per cent in the recurrent abortion group and 75 per cent in the prognosticated abortion group.

Does the use of estriol glucuronide, chorionic gonadotropin or thyroid substance alter the efficiency of progesterone therapy? The total success in the 54 patients was 57 per cent. Sixty per cent of the 38 patients who received estriol glucuronide went to term or are progressing satisfactorily. Pregnancies were maintained in 48 per cent of the 23 patients who received chorionic gonadotropin. Seventy-two per cent of the 29 patients who received thyroid substance went to term. From this analysis, it appears that neither estriol glucuronide nor chorionic gonadotropin is of therapeutic value. Thyroid substance does seem to enhance the efficacy of treatment when hypometabolism exists.

It is accepted generally that most spontaneous abortions occur about the time the second and third menses are missed. Theoretically, one might expect that the earlier the initiation of therapy in the patients treated prophylactically and the later the onset of symptoms in the patients threatening abortion, the better would be the prognosis. The apparent exception to this generalization is the patient who has passed through the time of maximum danger and who subsequently receives prophylactic treatment. Every patient in the prognosticated abortion group received therapy prior to the end of the 12th week. The maintenance of pregnancy in those patients of the recurrent abortion group who were placed on therapy prior to the end of the 12th week was 42 per cent (5 of 12) and was 75 per cent (3 of 4) in those patients placed on therapy after the 12th week. We

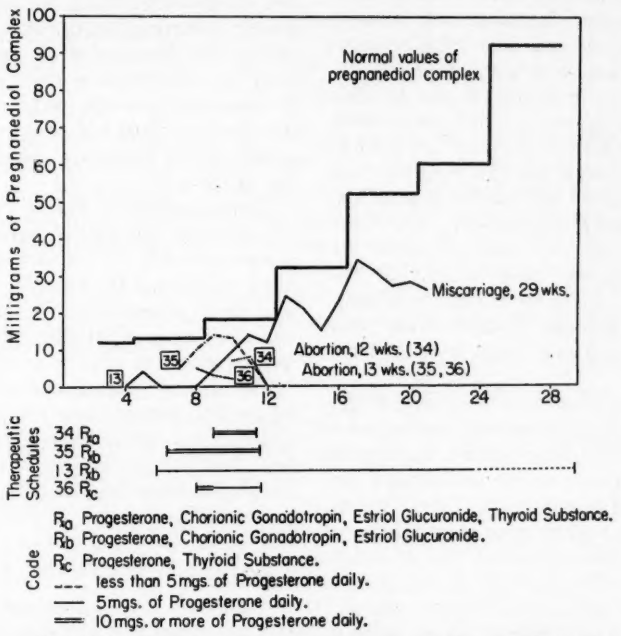

FIG. 3. URINARY EXCRETION OF PREGNANEDIOL-COMPLEX, therapy and clinical course of *patients 13, 34, 35, 36*. All of these patients aborted or miscarried. See figure 1 for explanation of pregnanediol-complex values. The values for these 4 patients were initially depressed.

had 92 per cent (11 of 12) success in treating threatening abortion when symptoms started after the 12th week and 33 per cent (6 of 18) success whem symptoms began before the end of the 12th week. The implications are obvious and these may explain partially the marked differences in our results from those reported in the literature.

Oral anhydrohydroxyprogesterone was used in 15 patients, initially in 8 patients and following therapy by injection in 7 instances. In no patient were there any symptoms of threatening abortion associated with the change from the injection to the oral form of therapy. It seemed that oral therapy was as efficacious as injection therapy. The dosage ratio between injected progesterone and oral anhydrohydroxyprogesterone has been assumed to be about 1 to 10.

Justification for the inclusion of the so-called prognosticated abortion group in this report seems obvious (11). An objective diagnosis of deficient ovarian function was made prior to pregnancy and there is reason to believe that the fertile state was brought about by therapeutic measures. The predication of a likely return of a state of ovarian deficiency during pregnancy seems warranted. The fact that 3 patients of this group who did have symptoms of threatening abortion (2 aborted) had these symptoms early in pregnancy tends to confirm this predication.

The urinary level of sodium pregnanediol glucuronide appears to be of prognostic significance in the pregnant woman (12). Four patients, in whom the pregnanediol-complex values were initially and continually low, aborted or miscarried. Three patients, in whom pregnanediol values were normal but were followed by zero or near zero values, aborted or miscarried within a few days after this sharp decline in the excretion of the pregnanediol-complex. Six of 7 patients with continually normal values went to term. The one patient in this latter group who did not go to term had premature rupture of the membranes during the 22nd week and miscarried during the 25th week.

The fact that the level of sodium pregnanediol glucuronide excretion could not be raised by the therapeutic use of progesterone (13) makes it impossible to use this method as a guide to therapy. Thus one of the sanguine expectations for the application of the method has not been established.

All obstetric patients studied by us have excreted some sodium pregnanediol glucuronide (14). Wilson, Randall and Osterberg (15) believe that the excretion of over 10 mg. of pregnanediol-complex is diagnostic of pregnancy. In 3 patients (*cases* 36, 34 and 13), the diagnosis of pregnancy would not have been established by these criteria as late as the 8th, 10th, 12th weeks respectively. Buxton (16) believes that the pregnanediol method has value in establishing a negative diagnosis. He states that, 'no pregnancy cases have been observed here or reported elsewhere, which had negative pregnanediol determinations.' One patient (*case* 13) is an exception, for zero levels were found during the 4th, 6th, 7th and 8th weeks of pregnancy. It is difficult for us to justify the use of the pregnanediol method to establish or rule out a diagnosis of pregnancy.

SUMMARY

The results of therapy for the prevention of abortion, progesterone being the common therapeutic element, is reported in 54 patients. Sixteen of these patients had histories of recurrent abortion; pregnancy was maintained in 50%. Thirty had histories of threatening abortion; pregnancy was maintained in 57 per cent. Eight had pre-gestational diagnoses of ovarian failure; pregnancy was maintained in 75 per cent of these.

Thyroid substance was an important adjunct, if not the major therapeutic factor, in patients with hypometabolism. The earlier that prophylactic therapy is started and the later the appearance of symptoms which necessitate active therapy, the better the results of therapy. Oral anhydrohydroxyprogesterone was apparently as efficient as injected progesterone.

The sodium pregnanediol glucuronide excretion values of 14 patients were studied. Six of 7 patients who excreted normal levels of pregnanediol went to term. Four patients who had initially and continually low levels aborted or miscarried. Three patients who had normal levels followed by zero or near zero values aborted or miscarried within a few days after the sudden drop in the pregnanediol excreted.

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Treatment of Prepuberal Vulvovaginitis with Diethylstilbestrol[1]

[Vulvovaginitis]

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From the Departments of Pediatrics and Gynecology, Tulane University of Louisiana, School of Medicine, New Orleans, Louisiana

IN 1940 (1) we presented a preliminary report of a series of 25 cases of infant vulvovaginitis treated by means of diethylstilbestrol administered orally. We have continued this investigation until the present and are able to present 124 cases so treated for critical review.

The greater majority of these cases have been followed more than one year, none less than three months and some more than two years.

MATERIAL

As in the previous report the material consists of cases of vulvovaginitis from the Departments of Pediatrics and Gynecology of Hutchinson Memorial Clinic, Charity Hospital Clinic, Touro Infirmary and some private cases. The youngest child treated was 2 months, the oldest, 12 years old. Of the total cases treated 92 were colored and 32 white (table 1).

In the earlier part of the study the diagnosis of gonorrheal vulvoganitis was based upon the finding of Gram-negative intracellular and extracellular diplococci in vaginal smears. In the last year we have used cultural studies as well as Gram-stained smears for diagnostic criteria. It is agreed that the results obtained by smear and culture are superior to those of smear or culture alone.

METHODS

As soon as the diagnosis was established, the child, irrespective of age, weight, duration of symptoms, severity of disease or previous therapy, was given 1 mg. of diethylstilbestrol[2] orally, three times a day, until 20 mg. had been administered. The tablet was crushed and administered in 2 oz. (60 cc.) of cow's milk. The usual prophylactic methods and instructions were given to the mother, but the only form of therapeusis used was the diethylstilbestrol. The longest period of time in which treatment was continued was 3 weeks, but this was necessary in only two cases. The great majority were treated for only 1 week.

Criteria of Cure. The criteria of cure were as follows. During the first year of study, smears were made weekly, until five consecutive negative smears had been obtained. At this point the child was considered cured. Smears were then made monthly and the child observed regularly in order to establish permanence of cure. In the last year of this study the smears have been supplemented by the use of cultures. Some of the children treated earlier were also checked by preparation of cultures. The cultures were made by Drs. Weiss and Colvin (2), Touro Infirmary, according to methods described by them. Any cases having consecutively negative smears and cultures for a period of at least 3 months were considered cured. Since we desired to check these children as frequently as possible for our own critical analysis we followed many for more than one year. Smears were studied for the presence or absence of the Neisserian diplococcus, pus cells and character of the epithelial cells present. The PH values were recorded in 50 patients by using nitrazine paper. The PH values reveal the fact that diethylstilbestrol is an agent

TABLE 1. CASES

Total cases	124
White	32
Colored	92
Youngest	2 months
Oldest	12 years

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[1] Aided by a grant from the Anonymous Research Fund, Tulane University.

[2] The diethylstilbestrol used in this study was supplied by the Winthrop Chemical Company, Inc., New York City, through the kindness of Mr. Kenneth Smoot.

whereby the normal alkaline PH of a child's vagina is quickly changed to a strongly acid reaction. The PH continues to be acid for about 4 weeks following discontinuance of therapy, and then it slowly becomes alkaline again (fig. 1). Vaginal biopsies and the presence of cornified epithelial cells with pyknotic nuclei

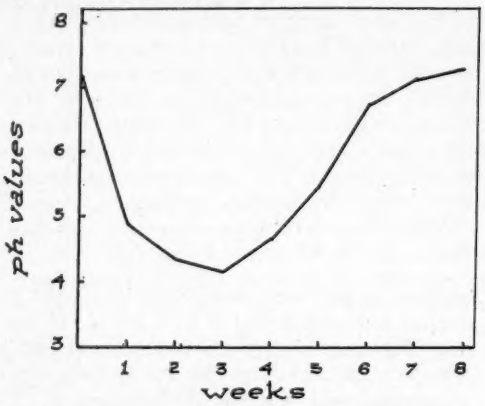

Fig. 1. COMPOSITE CURVE OF PH DETERMINATIONS OF 50 CASES OF INFANT VAGINITIS TREATED WITH DIETHYLSTILBESTROL

show that a transformation to an adult type of mucosa has taken place at the same time.

DISCUSSION OF RESULTS

In our earlier report we proved, by means of vaginal biopsy, that full estrogenic response was obtained in the vaginal mucous membrane, usually within a period of 7 days, by the administration of 1 mg. of diethylstilbestrol orally, three times daily. Coincident with the full estrogenic response, vaginal

TABLE 2. COMPLICATIONS

Pain about umbilicus	25
Nausea	6
Vomiting	8
Diarrhea	3
Swollen pigmented nipples	124
Edema of labia majora	22
Tender nipples	2
No complications other than pigmented nipples	84

smears showed the absence of pus cells and Gram-negative diplococci, only large epithelial cells containing much glycogen and small pyknotic nuclei being found.

These findings are in accord with the results obtained by administering estrogenic sterols in the form of vaginal suppositories, with the exception that usually 21 to 28 days are required to attain the same results when suppositories containing estrogenic sterols are used. Recently Woodruff and TeLinde (3) in a study of 50 cases of infant vulvovaginitis treated with diethylstilbestrol concluded that gonococcal vaginitis can be successfully treated with the synthetic estrogen, diethylstilbestrol. They found that 'the disease could be cured by oral administration as well as by suppositories, but our results were more uniformly successful and were obtained on an average more rapidly with the latter.'

We have not had any experience using suppositories of diethylstilbestrol in the treatment of infant vulvovaginitis. We are still using the same dosage of diethylstilbestrol, given over the same period of time and administered in the same manner as formerly, but it is planned to treat a series of cases using suppositories of diethylstilbestrol to compare the results with the present series. Experience with the larger series than was first reported gave no reason to vary the original plan. No patient was observed in whom toxic or unpleasant symptoms arising from the drug warranted its discontinuance. True, certain side effects were observed (table 2), but none was more than mild in nature and all regressed completely within two weeks following completion of therapy. The estrogenic response, as determined by the vaginal smear, usually persisted for a slightly prolonged period of time. No permanent change was observed in any patient, nor was any symptom observed that would make us hesitate to apply this form of therapy in any case of infant vaginitis.

TABLE 3. SMEAR AND CULTURE STUDY

Period Followed	Repeated Negative Smears Unconfirmed by Culture	Repeated Negative Smears Confirmed by Culture	Recurrent Reinfections	Failures	Inadequately Followed	Total Cases Followed
3 months	3	7	4	0	6	20
3–6 months	10	7	3	0	8	28
6 months–1 year	2	2	1	1	4	10
1–2 years	37	15	1	1	0	54
2 years	11	1	0	0	0	12
Total	63	32	9	2	18	124

Any case in which the patient failed to report for 5 consecutive weeks was considered to be inadequately followed even though all of the patients so classified had negative smears when last seen. There were a total of 106 cases with complete follow-up studies (table 3). Of this number 95 cures were obtained (90%), table 4. There were 9 cases of recurrences or reinfections and 2 failures. Of the recurrences or reinfections, all but 2 were cured by a

TABLE 4. PERCENTAGE OF CURES

Period of Treatment	Number of Cases	Cases Cured	Percentage Cured	Reinfection, Recurrence	Percentage of Recurrence	Failure	Percentage Failures
1 week	89	82	92	7	7	0	
10 days	9	8	89	1	11		
2 weeks	6	5	83	1	16	0	
3 weeks	2	0		0		2	100
Totals	106	95	90	9	8	2	2

second course of therapy. These two failures resisted attempts to obtain a cure by means of diethylstilbestrol or other types of therapy (table 5).

TABLE 5. RETREATMENT OF RECURRENCES, REINFECTIONS AND FAILURES

Cases Followed	Negative Smear, No Culture	Negative Smear, With Culture	Failure
Less than 3 months	0	0	0
More than 3 and less than 6 months	1	3	0
More than 6 months and less than 1 year	2	3	1
More than 1 year	0	0	1

Treatment Period	Cases	Cures	Recurrence	Failure
1 week	4	4	0	0
10 days	5	5	0	0
4 weeks	2	0	0	2

At the onset, the acute case of vulvovaginitis presented a thick, greenish yellowish discharge, which changed, within 36 to 48 hours after administration of diethylstilbestrol, to a thin mucous discharge. Smears and cultures made daily showed that the earliest negative smears and cultures were seen on the third day, and that a majority of cases presented negative smears and cultures 2 to 5 days following the administration of diethylstilbestrol.

CONCLUSION

1. After two years of experience in the use of diethylstilbestrol orally for the treatment of infant vulvovaginitis, we are as enthusiastic about its use as we were at the time of presenting our preliminary report.

2. We feel that diethylstilbestrol has definite advantages over other methods of treatment. They are: *a*) It can be administered orally. *b*) Cure is rapid and efficient. The length of time required for cure is far shorter than for any other method of therapy. *c*) The child is not rendered 'genital conscious,' and, in fact, is not aware that she is taking medicine. *d*) The expense is small. *e*) Its use provides an easy method for the control of possible widespread infection in institutions. *f*) The toxic effect is never enough to warrant discontinuance of the drug.

3. In the 106 cases considered adequately followed the rate of cure was 90%.

4. If the 18 cases are included who were negative at the time last seen, but who did not report for 5 consecutive weeks, the rate of cure is 122 of 124 cases, or 98 per cent.

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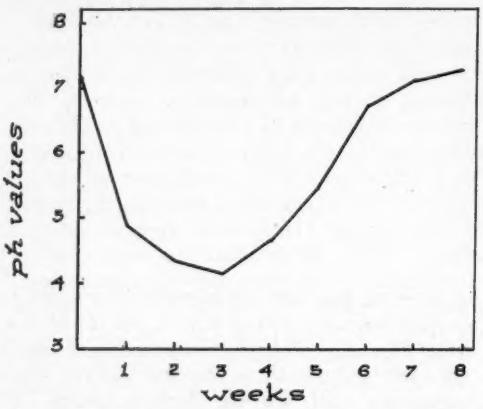

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Clinical Evaluation of Adjunctive Therapy with Stilbestrol Monomethyl Ether with Comments on Toxicity

[Stilbestrol Monomethyl Ether]

A. R. ABARBANEL, M.D.[1]

From the Endocrine Clinic of the Department of Gynecology, Harlem Hospital, New York City

THAT ALL biological processes are essentially chemical in nature is becoming increasingly evident, especially in the field of reproductive physiology. Among the more significant of these advances has been the demonstration that estrogenic activity is the property of scores of compounds, many of which do not possess a steroid nucleus. The latter group includes the very potent synthetic estrogen, diethyl-dihydroxystilbene, which is also known as diethylstilbestrol.

The ultimate desideratum of estrogenic therapy is a compound that is efficacious orally, inexpensive and practically free from side reactions. To date, diethylstilbestrol has proven to be the compound most suitably meeting these requirements. In a small percentage of patients certain undesirable side-effects may occur usually of a gastrointestinal nature. In an effort to reduce these side-effects to a minimum the compound stilbestrol monomethyl ether has been prepared and submitted for clinical trial.

Since it has been shown that estrone methyl ether is probably demethylated into free estrone before being metabolized, it seemed plausible that demethylation of stilbestrol monomethyl ether was a prerequisite for its estrogenic action (1, 2). By administration of the monomethyl ether of stilbestrol, it was hoped that only small concentrations of the more active stilbestrol would thus become available in the body at any one time.

In the rat Geschickter found that, orally, diethylstilbestrol was from 2.5 to 5 times as potent as stilbestrol monomethyl ether. By injection, diethylstilbestrol was about 6 times as active. When 10 to 25 times the threshold dose was injected, however, the effect of the monomethyl ether was maintained approximately 3 to 10 times as long (3).

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[1] Now with the Department of Obstetrics and Gynecology, George Washington School of Medicine, Washington, D. C.

CLINICAL EVALUATION

From December, 1940, to January, 1942, we have treated 120 patients. Approximately 96 per cent of these were colored.

Severe Climateric Vasomotor Instability

There were 97 cases in this group, of which 62 were surgical and 35 were spontaneous. The selection of patients was made in a manner previously described (4). Briefly, at the first visit the patient was carefully evaluated mentally as well as physically. If a history of nausea was elicited, an attempt was made to determine whether the nausea was caused by sensitivity to fried or fatty foods, or whether it was precipitated by the hot flashes, for it was found that many patients were nauseated with especially severe flashes. In addition, it was found that a small percentage of patients gagged on any type of pill, including lactose placebos.

For a period of 2 to 6 weeks each patient received sedation in the form of bromides or barbiturates. If the individuals were overweight, they were sent to a dietitian for advice. When indicated, the basal metabolic rate was determined. The patients were advised to avoid situations in which a strain would be placed upon the vasomotor system especially in regard to the heat regulating mechanism (5). In addition, each patient kept a daily written record noting separately the number of flashes experienced by day and after retiring at night. Placebos of lactose made up to look exactly like the tablets of stilbestrol monomethyl ether were frequently given both before and during therapy. When the drug was administered parenterally, injections of sterile oil or sterile water were often given both before and during the course of treatment. In this manner, it was possible to eliminate over 60 per cent of the patients who were sent to the Gynecological Endocrine Clinic with the diagnosis of 'menopausal syndrome.' Moreover,

TABLE 1. DOSAGE OF STILBESTROL MONOMETHYL ETHER REQUIRED TO BRING MENOPAUSAL PATIENT INTO VASOMOTOR EQUILIBRIUM[1]

Dose,[2] mg.	Interval	Route	Response[3]										Total Number of Patients
			None		Slight		Moderate		Good		Excellent		
			No.	%	No.	%	No.	%	No.	%	No.	%	
0.1	Daily	Oral	11	55	5	25	2	10	2	10	0	0	20
0.5	Daily	Oral	7	17	12	29	15	36	4	9	4	9	42
1.0	Daily	Oral	2	4	11	20	14	25	17	30	12	21	56
2.5	Daily	Oral	0	0	3	6	9	17	22	42	18	35	52
5.0	Daily	Oral	0	0	0	0	1	7	7	50	6	43	14
10.0	Weekly	Injection	1	4	4	15	10	37	9	33	3	11	27
25.0	Weekly	Injection	0	0	2	8	2	8	15	57	7	27	26

[1] Determined by the control of hot flushes.
[2] These do not represent maintenance doses.
[3] Response was graded as follows: *None*, no response; *Slight*, slight decrease in intensity of flushes; *Moderate*, definite reduction in number and intensity of flushes; *Good*, less than 5 mild flushes by day and occasionally one at night; *Excellent*, no flushes at night, occasionally one during the day.

any patient who did not have flushes or sweats at night was also excluded, for it was found in the majority of these cases that psychogenic factors were the principal precipitating cause. In short, only those cases which could be classed as 'severe' menopausal syndrome were treated. The occurrence of hot flushes was the criterion used in judging the response of the patient. All other symptoms were considered secondary.

If, in spite of adequate sedation and mental reassurance, flushes and sweats were not controlled, stilbestrol monomethyl ether[2] was administered. The patient was instructed to take the tablets after the morning or evening meal. When the history was suggestive of a gallbladder syndrome or chronic constipation, a teaspoonful or two of magnesium sulfate also was prescribed each night.

In table 1 are summarized the results obtained on the various dosage levels. It should be noted that these do not represent the maintenance dose necessary to keep the patient in a state of well being, but rather the dosage required to bring the patient into vasomotor equilibrium. At first the smallest available dose (0.1 mg.) was given for a period of 2 to 4 weeks; later as our experience increased, the starting dosage was increased. At present, 1 to 2.5 mg. daily is used as the initial dosage. The dosage was maintained or increased until the flushes or sweats were practically abolished at night, while, if they occurred during the day, they were both mild and infrequent. At this point a state of vasomotor equilibrium was considered as established. After a period of 3 to 4 weeks on the dosage necessary to establish equilibrium, the amount was gradually reduced, if possible, until a maintenance dose-level was secured. Peculiarly enough, it was found that the maintenance dose-level fluctuated in many patients. This was particularly evident when the weather was changeable, especially in the spring and fall. In addition, a psychic upset such as disagreement with a member of the family not infrequently disturbed the patient's vasomotor equilibrium. An attempt was made to keep the patient practically symptom-free for 3 to 6 months, or more, before discontinuing therapy.

In table 2 are analyzed the gastro-intestinal side-effects that were observed during therapy. From the correlation of reactions and dosage levels it is evident that the higher the dosage the higher the percentage of side-reactions (4, 6). Furthermore, patients with a previous history of sensitivity to fried and fatty foods were noted to be much more prone to experience nausea at any given dosage level. Similar observations have been reported with the use of diethylstilbestrol.

Bleeding occurred in 5 of the 35 cases of natural menopause. In two, it was scanty and irregular; menopause had occurred one and two years earlier, respectively. As a rule, bleeding appeared while the dosage was being lowered, but therapy was not discontinued. In the third case, bleeding occurred after therapy was stopped. In the remaining two cases, the bleeding proved to be troublesome. Both of these were still having periods at more or less regular intervals. One of these received 25 mg. by injection on the first day of an apparently normal menses. The flow increased markedly and 12 days later a curettage was performed. A well developed secretory endometrium was found. In the other patient, receiving 2.5 mg. daily, menses became more regular but much more profuse and lasted 8 to 10 days. Endometrial biopsy on one of these occasions disclosed a secretory endometrium. In both of these patients therapy was discontinued although the pelvic findings were essen-

[2] Diethylstilbestrol monomethyl ether (Monomestrol) was supplied by Drs. W. Salmon and F. C. Schmelkes of Wallace and Tiernan Products Company, Belleville, N. J. Diethyl stilbestrol (Estrobene) was supplied by Mr. A. A. Ebby of Ayerst, McKenna & Harrison, Ltd., Rouses Point, N. Y. Estradiol dipropionate (Di-Ovocylin) was supplied by Dr. E. Oppenheimer of Ciba Pharmaceutical Products, Inc., Summit, N. J.

tially normal. When methyl testosterone was given orally to these 2 patients the flushes were relieved. Bleeding, when it occurred, was normal in amount.

In summary, then, bleeding proved troublesome in two, or approximately 6 per cent of the treated cases of spontaneous menopause. It should be emphasized that bleeding may become an annoying symptom, but usually only in those patients who are still menstruating more or less regularly.

TABLE 2. COMPARISON OF GASTRO-INTESTINAL SIDE-REACTIONS EXPERIENCED BY PATIENTS WITH PREVIOUSLY NEGATIVE GASTRO-INTESTINAL HISTORY (*Group V*) AND THOSE NOTED IN PATIENTS WITH A POSITIVE HISTORY OF SENSITIVITY TO FRIED AND FATTY FOODS (*Group IV*)

Dose, Route, mg.	Total on Dose	Previous G.I. History	No. of Each	Nausea		Total with Nausea, %
				No.	%	
0.1, oral; daily	20	Negative	15	0	0	0
		Positive	5	0	0	
0.5, oral; daily	42	Negative	28	0	0	0
		Positive	14	0	0	
1.0, oral; daily	56	Negative	42	0	0	2
		Positive	14	1	7	
2.5, oral; daily	52	Negative	41	0	0	2
		Positive	11	1	9	
5.0, oral; daily	14	Negative	10	3	30	36
		Positive	5	2	40	
10.0 hypo.; weekly	27	Negative	18	1	6	7
		Positive	9	1	11	
25.0 hypo.; weekly	26	Negative	16	1	6	11
		Positive	10	2	20	

In 23 instances, it was possible to compare the effectiveness of stilbestrol monomethyl ether with diethylstilbestrol[2] orally. In 18 cases, mg. for mg., diethylstilbestrol proved to be approximately 5 times as effective as stilbestrol monomethyl ether.[3] The average for the group disclosed that diethylstilbestrol was 5.4 times as effective, comparing fairly well with experimental data (3).

[3] This was determined in the following manner. Patients were secured who were in fairly good vasomotor equilibrium, having from 2 to 5 flushes daily and rarely one at night. After 4 weeks on the same dose level of stilbestrol monomethyl either with no improvement, the therapy was changed to diethyl stilbestrol, using one-tenth the dose of the monomethyl ether. If necessary, the dose of diethyl stilbestrol was raised at two-week intervals until a more stable vasomotor equilibrium was reached and maintained. In a similar manner it was found in 4 patients that, dose for dose, estradiol dipropionate was 15 to 20 times as efficacious as stilbestrol monomethyl ether when administered intramuscularly in sesame oil.

Essential Senile Vaginitis

There were 7 patients in this group including one with mild generalized essential senile pruritis. In each case, after excluding all other constitutional and local causes, relief was secured mainly by local therapy. Once a week a tampon of non-absorbent cotton coated with 25 mg. of stilbestrol monomethyl ether in sesame oil was inserted and left in place for 48 hours. A douche twice a day with a quart of lukewarm water containing 8 tablespoons of household vinegar was prescribed following removal of the tampon.

The patient with the essential senile pruritis was 72 years old. The vaginitis was of about two years' duration and in the last 6 months it had become much more severe. During this time she observed that she had a generalized itch all over her body. Many scratch marks bore evidence to this. The vaginitis cleared up with local therapy. Dermatological consultation confirmed the diagnosis of essential senile pruritis. She was placed on a high vitamin, high caloric diet with no relief. On oral therapy with stilbestrol monomethyl ether, some relief was obtained with 1 mg. daily. The prescription was changed to oral diethylstilbestrol, 1 mg. daily, with complete alleviation of the itching. In the relief of essential senile pruritis, we had previously found that estradiol and testosterone were practically specific (7). This is the second case observed in which complete relief of the essential senile pruritis was obtained with diethylstilbestrol. We have found that pellets are the ideal method of administration since this condition requires continuous therapy (4).

Galactorrhea

There were 4 cases in this group. Two were cases in which abortion had occurred 8 and 10 months before, respectively. Two were of that rare group of cases of post-hysterectomy lactation. No evidence of pregnancy was noted in the surgical specimens. In one, a supravaginal hysterectomy and a left salpingo-oöphorectomy was done. The breasts filled and lactation occurred 10 days later. The other, from whom both ovaries and uterine fundus had been removed, began to lactate a week following the operation.

In each of these 4 cases, regardless of the dosage of stilbestrol monomethyl ether (up to 50 mg. weekly), the amount of breast secretion either remained the same or actually increased. In short, the estrogen was ineffective in suppressing lactation. Methyl testosterone and testosterone propionate also had no effect. Negative results have been observed also with diethylstilbestrol (8) and estradiol (9).

Primary Dysmenorrhea

There were 6 patients in this group. In 4 dysmenorrhea had been of a mild character until an at-

tack of pelvic inflammatory disease had aggravated it. In only one of this group of 4 was any relief secured. She received 25 mg. of stilbestrol monomethyl ether a week by injection throughout the cycle. As soon as therapy was discontinued, the periodic pains returned. Of the two uncomplicated cases, only one was fully relieved by 5 mg. daily. In this case, too, relief occurred only while on therapy. In short, the results were not entirely satisfactory.

Secondary Amenorrhea

There were 6 cases in this group. In only 2 was any degree of success achieved. The first of these patients, aged 20 years, had had very irregular menses for the past year. For the last 4 months she had been amenorrheic. On examination, an infantile uterus was found. She also complained of sterility since her marriage 9 months before. With thyroid up to 3 grains daily for 2 months, no menses appeared. She was then given 50 mg. of stilbestrol monomethyl ether weekly for 3 doses. Eleven days later she menstruated. This therapy was repeated with similar results. The third time she remained amenorrheic for 10 weeks. On examination she was found to be pregnant. Seven months later she delivered a normal female infant. The second successful result was in a patient given combined thyroid and estrogenic therapy for 4 months. The other 4 cases failed to respond. It should be noted that 3 of these cases had previously failed to respond to therapy with pregnant mare serum.

COMMENT

The results obtained with stilbestrol monomethyl ether in the management of the menopausal patients demonstrate that it is therapeutically effective orally. Since gastro-intestinal side-reactions occurred almost exclusively in the menopausal patients, it would be profitable to analyze them in detail. Careful study reveals that gastrointestinal side-reactions to diethylstilbestrol or other of the stilbestrol derivatives may be divided into 5 groups.

Group I consists of those individuals who are unable to take any sort of pill by mouth. They gag and are nauseated even on lactose placebos. In these patients no nausea was noted on injection therapy. Such instances as these are considered incidental side-reactions.

Group II includes those patients who become nauseated only while receiving simultaneously some other medication such as digitalis, intravenous neo-arsphenamine or ferric ammonium citrate. In other words, the nausea or vomiting cannot be blamed exclusively upon the estrogen, for any one of these other drugs alone may cause nausea. These instances also are not considered true side-reactions but as merely incidental ones.

Group III includes those patients who become nauseated or 'sick to the stomach' concomitantly with their flushes. This is particularly evident on arising in the morning, a type of 'morning sickness' in the menopausal woman. In each instance, simultaneous with relief from the hot flushes by suitable therapy, the nausea disappeared. Not infrequently the flushes may actually be accentuated at the beginning of therapy (5), thus aggravating the nausea. This type of response also does not fall in the category of true side-reactions.

TABLE 3. GASTRO-INTESTINAL SIDE-REACTIONS IN PATIENTS WITH PREVIOUS HISTORY SUGGESTIVE OF '*Gall Bladder Syndrome*' COMPARED WITH THOSE OF NORMAL PATIENTS

	No. of Cases	No. with Nausea	Ratio	Per Cent	x/σ[1]	Probability of Error
Previous history of 'gall bladder syndrome'	15	5	1:3	33	3.185	.0014
Negative G.I. history	82	5	1:16	6		
Total	97	10	1:10	10		

It should be noted that the factor of dose level has been excluded here on the basis that the "scatter" was fairly even especially on the higher dose levels.

[1] Pearl, R.: Medical Biometry and Statistics, Chap. X and XI, Second edition, 1930, Saunders, Philadelphia.

Group IV consists of those patients whose past history reveals marked sensitivity to fried or fatty foods, accompanied by nausea, vomiting, severe heartburn and eructation. Clinically these symptoms are suggestive of a 'gall bladder' syndrome. Fifteen patients gave such a history. Of these, 5 became nauseated on stilbestrol monomethyl ether. One patient, receiving 1 mg. daily, orally, experienced no further nausea following cholecystectomy. A second patient, who was taking 5 mg. daily orally, was relieved by reducing the dose; while taking 1 mg. of of diethylstilbestrol daily she experienced no nausea and at the same time was completely relieved of the flushes. The remaining 3 patients were relieved of the nausea by taking either two teaspoonfuls of magnesium sulphate or 100 mg. of desoxycholic acid nightly. One of these patients was nauseated by 5 mg. daily by mouth and 25 mg. weekly by injection. A second one was nauseated by both 25 mg. and 10 mg. weekly.

Group V is made up of those patients with a negative gastrointestinal history who develop nausea only while receiving estrogenic therapy. In this series, there were 5 cases. In 2, the nausea was inconstant and disappeared in time. Two others were relieved

by reducing the dosage and gradually increasing it again. The fifth was relieved by changing from hypodermic to oral therapy.

When we exclude the patients in *Groups I, II and III*, we note that there were 10 patients with true gastro-intestinal side-reactions. Of these, 5 were of the group who gave a previous history suggesting a 'gall bladder syndrome.' The data are summarized in table 2. It is noted that patients giving a previous history suggestive of a gall bladder syndrome are much more prone to experience nausea, than those with a negative gastro-intestinal history. Statistical analysis (table 3) reveals that these figures are significant, even for various dose levels. Similar observations in patients receiving diethylstilbestrol have been reported (4). The explanation for the greater tendency of patients in *Group IV* ('gall bladder' syndrome) to experience nausea remains to be found. In the guinea pig it has been shown that estrogen will cause a delay in the emptying time of the gall bladder (10, 11). Such an effect, if proven in the human female, would account for the increased sensitivity to estrogens in patients of the type in *Group IV*. It would also explain the correlation between the higher dosage, and the greater incidence of side-reactions.

TABLE 4. INCIDENCE OF NAUSEA ENCOUNTERED AT VARIOUS DAILY ORAL DOSE LEVELS OF DIETHYLSTILBESTROL AND STILBESTROL MONOMETHYL ETHER[1]

Dose, mg.	Incidence of Nausea, %	
	Diethyl stilbestrol	Stilbestrol monomethyl ether
0.1	1.3	0
0.25	3.4	
0.5	5.3	0
1.0	12.1	1.8
2.5		1.9
5.0	41.7	35.8

[1] In making the comparison it should be noted that, orally, diethylstilbestrol is at least 5 times as potent as stilbestrol monomethyl ether.

Another factor of considerable importance in evaluating the side-reactions under discussion is the relative estrogenic potency of the substance in question. For example, in this diethylstilbestrol was found to be about 5 times as potent, mg. for mg., as stilbestrol monomethyl ether. When the incidence of side-reactions to both substances is compared on a potency basis, it is found to be essentially the same (table 4). Similar observations have been noted by others (6, 12).

Galactorrhea. The physiologic pathology of this condition is still not clear. On the basis of our present knowledge, the reason for the failure of diethylstilbestrol or the monomethyl ether of stilbestrol to affect the secretion may be hypothesized. Diethylstilbestrol may stimulate the increased production of lactogenic hormone by as much as 226 per cent (13). Thus, indirectly diethylstilbestrol actually stimulates lactation. In fact, lactation has been initiated in virgin goats (14), and partially, in the human female (15), by the use of diethylstilbestrol plus active massage or pumping of the mammary gland.

Essential senile pruritis. Just recently this syndrome was declared to be one of the unsolved problems of medicine (16). Preliminary experience with estradiol and testosterone demonstrated that these steroids were extremely effective in relieving pruritis. Our preliminary findings with diethyl stilbestrol and the monomethyl ether of stilbestrol, if confirmed, should prove a boon to patients with essential senile pruritis.

Oral mucous membrances. Pre-treatment biopsies of the buccal mucous membrane revealed varying degrees of atrophy in some patients. After adequate treatment the buccal mucosa showed the same histological picture of estrogenic stimulation as did the vaginal mucosa. These studies will be reported in detail elsewhere (17).

In its broader aspects, these are two more examples of the fact that the so-called sex hormone substances are fundamentally constitutional drugs, irrespective of their effects on the secondary sexual apparatus.

SUMMARY AND CONCLUSIONS

Adjunctive therapy with stilbestrol monomethyl ether, as with other estrogens, has shown that it is *a*), of definite value in the managment of climacteric vasomotor instability and senile vaginitis including essential senile pruritis; *b*) it is of very limited value in the management of secondary amenorrhoea and dysmenorrhea; and *c*), it is of no value in management of galactorrhea.

Analysis of gastro-intestinal side-reactions to therapy with stilbestrol monomethyl ether reveals that the greater the dosage, the greater the incidence of side-reactions. Patients with a previous history of sensitivity to fried and fatty foods are more prone to suffer nausea than are patients with a negative gastro-intestinal history. When stilbestrol monomethyl ether is compared with diethylstilbestrol on a potency basis, the incidence of nausea is similar if given orally.

In 35 cases of spontaneous menopause receiving treatment with stilbestrol monomethyl ether bleeding proved to be troublesome in two or 6 per cent.

An atrophic buccal mucosa was proved by biopsy to be restored to normal after treatment.

Orally, diethylstilbestrol was found to be at least 5 times as potent as the monomethyl ether of stilbestrol.

When injected in sesame oil, estradiol dipropionate was found to be from 15 to 20 times as potent as stilbestrol monomethyl ether, mg. for mg.

The author is indebted to Drs. P. E. Crooks and E. Matlin for their kind assistance in carrying out these studies.

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Effect of Inunction of Alpha Estradiol and of Oral Medication with Pregneninolone upon Postmenopausal Human Uterus

[Postmenopausal Endometrium]

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NEUSTAEDTER (1), using 120 mg. of synthetic α-estradiol and 900 to 1200 mg. of pregneninolone, both given by mouth, was able to produce proliferation and subsequent secretory changes in the endometrium of 6 women, ranging in age from 22 to 40 years, who had been surgically castrated.

The present study was made to determine whether similar changes could be produced in women in the menopause after bleeding had ceased spontaneously for a considerable length of time, in these instances, from 1 to 7.5 years, and in whom marked atrophy of the uterus, cervix and vagina was present.

Six patients were studied. All had atrophic or resting endometrium prior to treatment. In 3 cases there was such a marked atrophy of the endometrium that it was impossible to obtain endometrial tissue for premedication biopsies, even after vigorous curettage. The patients were given an ointment containing 1 mg. of synthetic α-estradiol per gm. of ointment, and were instructed to use it by inunction, from 1 to 2 gm. daily for 1 month. After 2 weeks they were given 100 to 120 mg. of pregneninolone orally per day for 10 days. In two of the cases the course of therapy was repeated.

Subsequent endometrial biopsies revealed the following: *a*). After 2 weeks of estradiol therapy by inunction, endometrial biopsy specimens from each of the 6 cases revealed proliferation of the endometrium. *b*). After combined estradiol inunction and oral pregneninolone therapy, the endometrium in 4 of the 6 cases showed secretory changes.

The 6 patients had suffered from menopausal symptoms, mild to severe in degree, consisting of flushes, sweats, headaches, and nervousness, for some time. These complaints were completely relieved during the course of therapy. However, after cessation of treatment, these symptoms recurred, usually within 5 to 10 weeks.

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CASE REPORTS

Case 1, R.F., aged 49, white female, married, having 3 adult children. Onset of menses was at 14 years, with 3-day periods of moderate flow, associated with dysmenorrhea, occurring regularly every 28 days. Menopause with rather severe symptoms, consisting of flushes, sweats, vertigo, and headaches, began 18 months previously. Last bleeding episode was in July, 1940. The last previous bleeding took place in November, 1939. Basal metabolic rate was −14 per cent. Hormone study revealed a negative prolan reaction and 8.5 R.U. of estrin per 24-hour specimen. A biopsy performed on May 6, 1941 demonstrated almost complete atrophy of the endometrium, and no tissue was obtained. On May 13, biopsy produced an endometrial mucosa with an occasional gland. A diagnosis was made of a very early proliferative phase. Estradiol ointment, 2 gm. daily, was given between May 13 and June 3. On June 3 the biopsy report indicated an early proliferative phase, more advanced than in the previous biopsy. Estradiol ointment, 2 gm. per day, combined with 100 mg. of pregneninolone orally was given daily for 10 days, from June 3 to 12, at which time the patient began to bleed, and stained for 6 days. The biopsy made at the beginning of bleeding revealed a late proliferative and early secretory phase. The patient felt very well at this time, and had no complaints. Her condition continued satisfactory for 6 weeks, by which time she was again suffering from some menopausal symptoms.

Case 2, L.M., aged 53, white female, married, para ii. Onset of menses was at 14 years, with 4-day periods of moderate flow, without pain, occurring regularly every 28 days. The last menstrual period was 7 years ago, at which time menopausal symptoms began. The basal metabolic rate was +4 per cent. Hormone determinations revealed a positive prolan and a negative estrin reaction. On examination, the uterus was found to be 2.5 inches long, anterior, firm and freely mobile. No adnexal pathology was present. An endometrial biopsy was made on May 8, 1941 and no tissue was obtained. Between May 8 and May 15, estradiol ointment, 1 gm. daily, was administered by inunction. On May 15, a biopsy specimen of the endometrium showed an early proliferative phase.

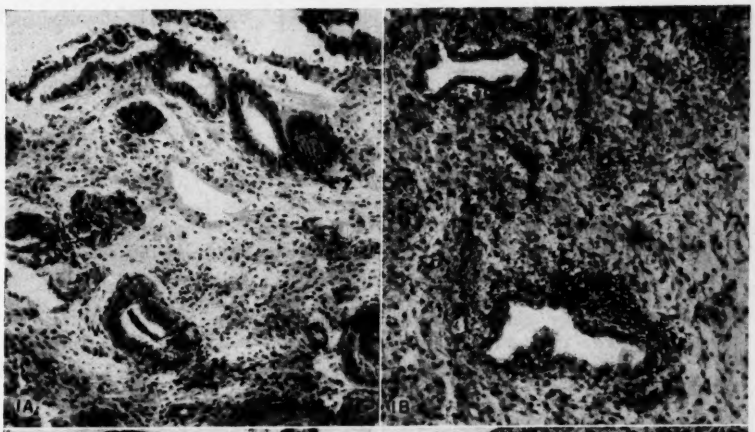

FIG. 1, A AND B. RESTING AND EARLY SECRETORY PHASE, respectively, of endometrium of *case* 3, before and after therapy.

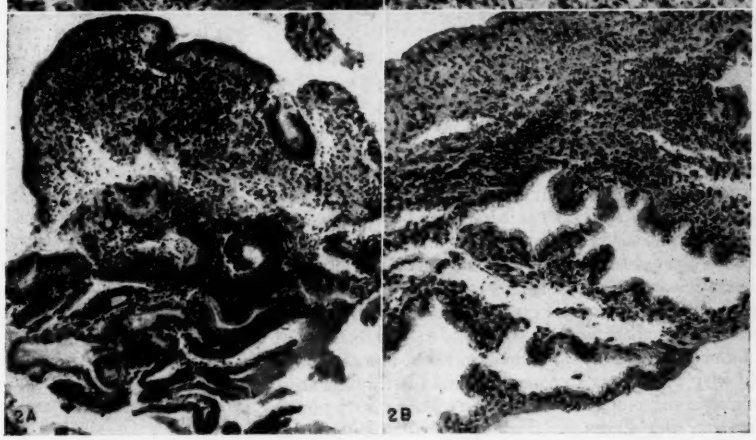

FIG. 2, A AND B. RESTING AND LATE SECRETORY PHASE, respectively, of endometrium of *case* 6, before and after therapy.

From May 15 to June 5 estradiol ointment, 2 gm. daily, was used; on June 5 a biopsy specimen of the endometrium revealed an early proliferative phase more advanced than in the previous specimen. Between June 5 and June 17, estradiol ointment, 2 gm. daily, and 100 mg. of pregneninolone daily, were given for 12 days. On June 17, an endometrial biopsy showed a proliferative reaction. The menopausal symptoms were entirely controlled at this time. Another course of therapy was given. From June 19 to July 10, estradiol ointment, 2 gm. daily, and between July 11 and July 21 estradiol ointment, 2 gm. and 120 mg. of oral pregneninolone, were administered for 12 days. Biopsy of the endometrium still indicated a proliferative phase. The patient's menopausal flushes, sweats, headaches, and nervousness had disappeared, and 2 weeks thereafter she was still symptom-free.

Case 3, *D.T.*, aged 43, white female, married, para i. Onset of menses was at 12 years, with 4-day periods of moderate flow, without pain, occurring regularly every 28 days. The patient had her last menstrual period 1 year ago, and simultaneously climacteric symptoms consisting of sweats, flushes, vertigo, and headaches had set in. Hormone determinations showed a positive prolan, and negative estrin reaction. Pelvic examination revealed the uterus to be 2.75 inches long, and retroverted. There was no adnexal pathology. On March 6, 1941 an endometrial biopsy was made but very scant shreds of tissue which were insufficient for diagnosis were obtained. From March 6 to March 27 estradiol ointment, 1 gm. daily was administered by inunction, and biopsy of the endometrium at this time demonstrated a proliferative reaction (fig. 1, A). Between March 27 and April 10 estradiol ointment, 2 gm. daily was given and from April 11 to April 22 estradiol ointment 2 gm. and 100 mg. of pregneninolone were administered daily for 11 days. On April 24, an endometrial biopsy was performed and an early secretory phase was found (fig. 1, B). The patient stated that she felt fine, and was asymptomatic. The patient continued without complaints when last seen, on July 24, 1941.

Case 4, *R.F.*, aged 43, white female, married. Onset of menses was at 12 years, with 3-day periods of moderate flow without pain occurring regularly every 28 days. The patient had had 2 full-term pregnancies. Severe menopausal symptoms consisting of frequent flushes, sweats, vertigo and occipital headaches started 1 year ago. The last bleeding episode occurred in July, 1940. Basal metabolic rate was −7 per cent. Hormone analyses showed that urinary prolan was positive, estrin negative. A biopsy

made prior to treatment showed an early proliferative endometrium. Pelvic examination revealed the uterus to be 2.5 inches long, anterior and freely movable. No adnexal pathology was demonstrable. Estradiol ointment, 1 gm. daily, was given by inunction from Dec. 12, 1940 to Jan. 13, 1941. Then estradiol ointment, 1 gm. and 10 mg. of pregneninolone daily, was administered for 11 days. On Jan. 23, an endometrial biopsy demonstrated an early proliferative phase, but more advanced than in the original biopsy. The course of therapy was repeated, using larger doses of pregneninolone. From Jan. 23 to Feb. 6 estradiol ointment, 2 gm. daily, was used by inunction, and between Feb. 6 and Feb. 17, estradiol ointment 2 gm. plus 100 mg. of pregneninolone were administered. An endometrial biopsy made on Feb. 17 revealed a late proliferative and early secretory phase. A third course of therapy was instituted, similar to the second, treatment being continued from June 24 to July 17. On this latter date, and after the patient had been bleeding for 5 days, the endometrial biopsy showed a resting endometrium.

Case 5, F.L., aged 44, married for 11 years, para i. Onset of menses was at 13 years, occurring regularly every 28 days, the flow was moderate in amount and painless. the patient had her last menstrual period 1 year ago, when climacteric symptoms of moderate degree set in consisting of sweats, flushes and headaches. Pelvic examination revealed the uterus to be 2.5 inches long and freely movable. There was no adnexal pathology. The basal metabolic rate was +9 per cent. Hormone determinations demonstrated a negative prolan and a negative estrin reaction. An endometrial biopsy was made on May 6, 1941, and an early proliferative phase found. From May 6 to May 27 estradiol ointment, 1 gm. daily, was administered by inunction, and on May 27 a biopsy specimen revealed a late proliferative phase in the endometrium. Between May 27 and June 5 estradiol ointment, 1 gm. and 100 mg. of pregneninolone were given daily, for 10 days. A biopsy taken on June 5 indicated an early proliferative phase in the endometrium. On June 6 bleeding occurred and lasted 3 days. The course of therapy was repeated, except that 120 mg. of pregneninolone daily was administered along with the estradiol. On July 15, at the end of treatment, an endometrial biopsy showed areas of marked proliferation. The patient's menopausal symptoms were completely controlled by this time. On July 18, bleeding took place. Menopausal complaints recurred 5 weeks after cessation of therapy.

Case 6, M.G., aged 51, married for 26 years, had 5 children and 4 miscarriages. Onset of menstruation was at 11 years, with 4-day periods of moderate flow, without pain, occurring regularly every 28 days. Last menstrual period was in October, 1940. Pelvic examination revealed the uterus to be 3 inches long, retroverted and freely movable. No adnexal pathology was present. Basal metabolic rate was −13 per cent. The hormone tests showed a positive prolan and negative estrin reaction. The vaginal smears indicated a marked deficiency in estrogenic activity. An endometrial biopsy was made on May 6, 1941 and an early proliferative phase found. From May 6 to May 27 estradiol ointment, 1 gm. daily, was administered by inunction. On May 27, a biopsy of the endometrium revealed a more advanced proliferative phase than in the tissue obtained on May 6 (fig. 2, A). Between May 27 and June 5 estradiol ointment, 2 gm., plus 100 mg. of pregneninolone, were given daily for 10 days. Endometrial biopsy performed on June 5 demonstrated an early secretory phase (fig. 2, B). During this time the patient suffered no menopausal symptoms. Vaginal bleeding occurred from June 7 to June 11, and was moderate in amount. On July 3 the patient complained that the menopausal symptoms were recurring, and on July 10 vaginal bleeding took place again. By this time the headaches, sweats, flushes and nervousness were quite severe.

COMMENT

Salmon, Walter, and Geist (2) produced progestational reactions in the endometrium of 5 postmenopausal women using doses of pregneninolone ranging from 105 to 540 mg. The endometrium in each case was first primed with from 120,000 to 655,000 R.U. of estradiol benzoate, injected intramuscularly.

Neustaedter produced progestational changes in the endometrium of 6 surgically castrated women with 1200 mg. of pregneninolone, given by mouth. The uteri were first primed with 120 mg. of synthetic estradiol, likewise administered orally.

In the present series of cases of 6 women, by giving adequate doses of pregneninolone, progestational changes in the endometrium were obtained in 4 cases after a preliminary period of priming by inunction with synthetic estradiol.

SUMMARY

1. Six postmenopausal women were treated with synthetic estradiol by inunction and pregneninolone orally. An average of 45 to 60 gm. of estradiol ointment, containing 45 to 60 mg. of the hormone, and 1000 to 1200 mg. of pregneninolone were used.

2. A proliferative reaction was produced in the endometrium in all 6 cases following estradiol inunction.

3. Following the combined administration of estradiol by inunction and pregneninolone orally, 4 of the 6 cases showed definite secretory changes in the endometrium.

4. All menopausal symptoms disappeared during the course of treatment.

5. Five to 10 weeks after cessation of treatment menopausal symptoms recurred.

6. All patients bled 1 to 3 days after cessation of treatment.

We wish to thank Dr. L. Pirk of Roche-Organon, Inc. for the supply of estradiol ointment, which was especially prepared for our purposes, and for the pregneninolone (Progestoral), the two preparations used in this study.

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Simmonds' Disease:
Report of Two Cases Caused by Intracranial Tumors

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BETWEEN 1914, when Simmonds first suggested that the clinical syndrome now named for him is the result of severe hypofunction of the anterior lobe of the pituitary, and 1940, when Escamilla and Lisser (1) reviewed the literature and their own practice, 595 cases have been diagnosed Simmonds' disease. Of these, only 101 were proved by necropsy. Although many of the other cases seemed typical clinically, analysis of the reported data led these authors to suspect that they were really examples of anorexia nervosa (1). The latter condition, they and others (2, 3), have considered most difficult to differentiate from hypopituitarism. Indeed, a chief purpose of their extensive review (1) was to establish criteria for differential diagnosis. In this connection, *Case 1* is interesting, as at first the diagnosis of anorexia nervosa seemed well established.

Stephens (4) has recently pointed out that the sodium deprivation regimen described by Cutler, Power, and Wilder (5) as a test for Addison's disease can be useful in establishing the diagnosis of Simmonds' disease because of the secondary type of adrenocortical insufficiency present in these cases. Sheehan (6) and others (7) have reported that hypopituitarism may simulate myxedema and have warned that such cases may be dangerously susceptible to the action of thyroid. From this viewpoint, *Case 2* is of interest, as the diagnosis of Addison's disease was made early in the course of his illness; was apparently confirmed by salt deprivation; and was evidently improved by desoxycorticosterone acetate. He, also, presented features suggestive of hypothyroidism and for a prolonged period had a favorable response to thyroid medication.

CASE REPORTS

Case 1. J.D., an 18-year-old, white male, was admitted on July 26, 1940, complaining of loss of weight and polyuria during the past year.

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Past history. Enuresis had been present since infancy. At 5, he contracted scarlet fever, followed in succession by measles, pertussis, cervical adenitis, which required incision and drainage, and otitis media. Thereafter, he remained in good health until the onset of his present illness, although he never gained weight satisfactorily.

Social history. The patient's mother died when he was 6. Until he was 12, he did fair work in school, being cared for during this time by his grandmother. Then his father remarried, and the patient exhibited deep resentment toward his stepmother. At the same time, his school work deteriorated, and he became a behavior problem. He associated with a bad gang, truanted, engaged in petty thievery, resorted to masturbation, lost interest in school, and was eventually expelled in the middle of the ninth grade. At the age of 16, he was referred to the Judge Baker Guidance Center, where he was noted to have an I.Q. of 99, to be 17 per cent underweight, to be slow in pubertal development, to have defective vision and headaches after reading, as well as frequent nocturnal enuresis. After leaving school the patient worked intermittently as a soda fountain clerk.

Present illness. In the summer of 1939 the patient first noted that he was passing an unusually large volume of urine, that his enuresis was more constant, and that his fluid intake was excessive. However, he felt well until early fall, at which time he weighed 125 lb., his peak weight. Height was 5 feet, 8½ inches.

He then began to vomit after nearly every meal without any abdominal pain or obvious cause. Weight loss soon became alarming. He was admitted to two other hospitals for study, but no reason for the vomiting was discovered. At times he would improve, but, except for cessation of enuresis in January, 1940, his condition remained little changed until admission to the Massachusetts Memorial Hospital, at which time he weighed 93½ lb. (42.5 kg.). Prior to admission, partial control of his polyuria had been achieved with pitressin by subcutaneous injection, but this caused abdominal cramps and further vomiting.

Physical examination. The patient was fairly well developed, but extremely thin. He was coöperative, well oriented, and able to give a good account of the details of his illness and of the treatment he had received. Skin was rough, cool, and dry. Hair on the head was red, dry, and abundant. Hair on the body was very scanty. A few, fine,

light hairs were present on the forearms and legs; axillary hair was almost non-existent; and pubic hair was sparse, light, short, and confined to a small area. Pupils reacted normally. There was no apparent visual disturbance. Ophthalmoscopic examination showed discs that were questionably pale; fundi were otherwise not remarkable. Lungs, heart, and abdomen were not abnormal. Reflexes were present in the arms, but in the legs the reflexes were very sluggish and could not always be elicited, although there were no pathological reflexes. Blood pressure was 82 mm. Hg, systolic and 48, diastolic.

Laboratory data. When the patient was not taking posterior pituitary the urinary specific gravity ranged generally between 1.002 and 1.004. Otherwise, the urine was not remarkable.

Hinton reaction on the blood was negative. Hemoglobin was 85 per cent on admission with red blood cell count of 4.2 million, and white blood cell count of 11,800 with 72 per cent polymorphonuclears, 22 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophils. During his stay, hemoglobin dropped to 70 to 75 per cent with red cell count ranging around 3.5 million. White cell count remained normal, but there was a gradual development of a lymphocytosis that persisted until discharge. During his last 3 months in the hospital, he showed an eosinophilia of from 2 to 5 per cent.

Oral glucose tolerance test with 100 gm. of glucose on 7/29/40 gave values in mg. per 100 cc.: fasting, 90; 30 min., 150; 2 hours, 150; 3 hours, 183; 4 hours, 90. Repeated on 11/20/40, the values were: fasting, 91; 1 hour, 138; 2 hours, 88; 3 hours, 102.

Total protein on 8/29/40 was 5.1 gm. per cent; albumin, 3.8 gm. per cent, and globulin, 2.35 gm. per cent. Blood cholesterol was 194 mg. per cent.

Basal metabolic rate was always low. Extreme ranges were from minus 37 to minus 17 per cent. Roentgen rays of the skull showed no evident pathology.

Clinical course. As can be seen in figure 1, the patient's urinary output was definitely in excess of his fluid intake during his first 18 days in the hospital. During this period he ate very little, vomited occasionally and lost weight slowly but steadily. He was very lethargic mentally and physically, seeming quite content to lie motionless in bed for long periods. Although he answered questions readily, his conversation was very superficial. It was impossible to interest him in anything. He had no expressed desire to regain his health. During this period, fasting blood sugar at the beginning and end of a 36-hour fast was 70 mg. per cent.

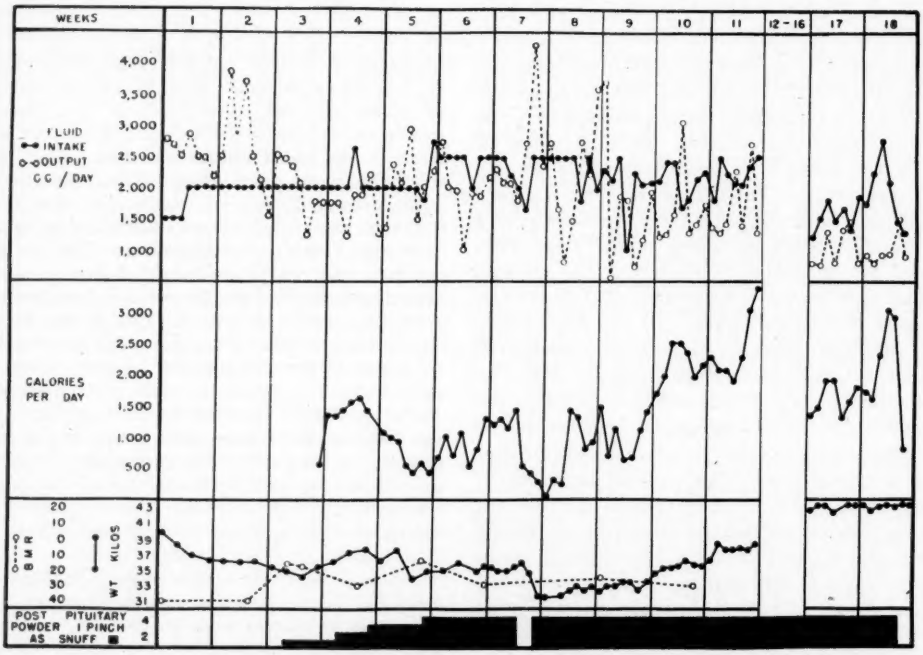

FIG. 1. *Case 1.* SUMMARY OF FLUID AND CALORIC BALANCE in relation to the use of posterior pituitary powder.

Patient was now given posterior pituitary powder by nasal insufflation. There was an immediate response. Urine output decreased. Vomiting stopped and appetite improved. Weight increased slightly, but steadily. Two weeks later, however, the powder appeared to lose its effectiveness. Subcutaneous injections of pitressin were tried for two days. This controlled urine output, but vomiting recurred, appetite failed sharply, and weight dropped. The patient complained of abdominal cramps,

and the descending colon and sigmoid could be felt as a tender, hard cord. Powder by nasal insufflation was resumed with increased dosage, and again he responded favorably.

Two weeks later the supply of posterior pituitary powder became exhausted, and all untoward symptoms recurred. At this time some whole gland pituitary powder was substituted without noticeable effect. Readministering posterior pituitary powder gave the same dramatic results as previously. He now began what proved to be a persistent improvement, which coincided with the institution of a regimen designed to stimulate his interest in his surroundings. He was obliged to have a hot tub bath every morning and to stay up most of the day. He was given light ward duties and was made to complete them.

During his first 3 weeks in the hospital, the patient was offered a high vitamin, high calorie diet with added brewer's yeast tablets (2.4 gm. daily). He took very little of his diet and by the 18th day his tongue was a beefy red. Addition of nicotinic acid (0.24 gm. daily) was soon followed by reversion of the tongue to normal. One month later, nicotinic acid was stopped for 5 days. Again, the tongue became red and raw looking, and again reverted to normal with resumption of the vitamin. About the same time, fissures became evident at the corners of the mouth along with cracks on the lips and a tendency to scaling. Riboflavin (4 mg. daily) was given with a very gradual improvement. Because it was thought that the roughening of the skin might be the result of vitamin A deficiency, he was given percomorph oil (3 capsules daily) beginning in his third week. The vitamin A level in the blood was determined somewhat later and reported as normal, but there was never any change in the skin. His cevitamic acid intake was always adequate.

After the second month had passed, improvement became steady, continuing until discharge on 11/27/40. At this time, he weighed 43.6 kg., which was a gain of 11.3 kg. over his low point reached at the end of his first month and one half, but only 3.6 kg. more than his weight on admission. He felt well, had a good appetite, was coöperative and cheerful, and appeared to have regained his interest in life. His urinary output and thirst were well controlled by four pinches of posterior pituitary powder, taken as snuff, daily. The discharge diagnosis was anorexia nervosa, diabetes insipidus, and multiple vitamin deficiencies.

The patient remained at home for a month and 17 days. Shortly after discharge, however, he began to vomit and to complain of an uneasy feeling in his stomach shortly after eating. He frequently felt weak and listless and had to be urged to get outdoors. Urinary output remained well controlled, and it was thought that he was finding it difficult to adjust to life at home. Finally, it became apparent that he was slipping backward, and on 1/14/41 he was readmitted for further study.

At the time of admission he weighed 41.7 kg. Physical examination was generally as before. However, he was even more listless than at the time of his first admission, and he complained of his vision. At first it was thought that he required new glasses, as his eyes had not been refracted for several years. Closer questioning brought out the fact that while at home he had noted that he had difficulty in making out objects across the street, or in recognizing his friends until they were very close. Also he had found that writing was awkward because of apparent double vision and because the pencil would vanish from sight when in certain positions. Visual fields (fig. 2) done on the Bjerrum screen, revealed total loss of vision in the lower temporal quadrant on the left and nearly total loss in the same quadrant on the right. Closer examination of the optic discs showed slight pallor, especially of the temporal portions. Stereoscopic roentgenograms of the skull were repeated and compared carefully with films taken in August and October, 1940. No evidence of any abnormality of the sella turcica could be found. The only possible abnormality noted was a doubtful backward displacement of the pineal gland.

Lumbar puncture yielded clear fluid under normal pressure and no evidence of block. Eighty-nine cells per

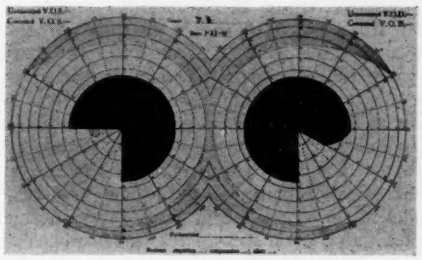

FIG. 2. *Case 1.* VISUAL FIELDS.

cu. mm., 50 per cent of which were polymorphonuclears, were found. Total protein was 112 mg. per cent. It was thought that the patient had a suprasellar tumor, probably a craniopharyngioma, and he was transferred to the Neurosurgical Service of the Boston City Hospital for treatment. It was noted before transfer that the diabetes insipidus was less severe than previously, required less posterior pituitary powder for control, and that he occasionally had a rise in temperature to 99° or 99.6° F. without evident reason.

He remained at the Boston City Hospital from 2/12/41 to 4/9/41. Because of his poor condition, surgery was withheld. Despite all efforts, he lost weight steadily and remained completely lethargic. Visual fields were checked frequently and remained the same except for the addition of a lower right nasal quadrantic field defect. Roentgenograms of the skull showed the pineal gland displaced to the right and slightly posteriorly. An insulin tolerance test with 3 U of regular insulin intravenously gave values in mg. per 100 cc.: fasting, 85; 20 minutes, 62; 30 minutes, 60; 45 minutes, 71; 60 minutes, 72; 90 minutes, 87; 120 minutes, 86. Urinary 17-ketosteroids were 2.5 mg. per 24 hours. Other laboratory data were the same as previously.

As he was considered too poor a risk for surgery, he was returned to this hospital on 4/9/41, at which time he weighed 32.1 kg. During the first week he gained 2 to 3 kg., but soon began to lose once more. During the third week vomiting became troublesome and at times almost

projectile in character. Tube feeding was resorted to but on the twenty-third day he lapsed into coma. Temperature which had not previously exceeded 100° (by rectum), began to rise steadily, reaching 107° F. 5 hours before death.

Necropsy. (Performed 5 hours and 15 minutes after death.) *Brain.* Weight, 1150 gm. The convolutions with intervening sulci and fissures were normal. At the base immediately posterior to the optic chiasm and intimately nestled between the optic tracts and mammillary bodies, which were distorted, was a thin-walled cystic structure, 2.5 cm. in diameter. This was an integral part of either the tuber cinereum or the pituitary stalk, and had no connection with the third ventricle. The vessels at the base of the brain were not remarkable. The lateral ventricles were markedly dilated and the cortex was somewhat thinned by a large accumulation of slightly turbid, watery fluid, which was distinctly flocculent and purulent in the dependent portion of the ventricles. A soft, light pinkish to grayish-brown, almost mucoid material, which was adherent to and apparently part of the ependymal surface, lined both anterior horns. This was 2 to 3 mm. thick and sharply demarcated from the adjoining white matter. The same type of material was present to a small degree on the surface of the third ventricle and to a greater extent on the floor of the fourth ventricle. Sections throughout the rest of the brain showed no gross abnormalities.

Microscopic sections through the brain, including portions of the ependymal lining, revealed a thin margin infiltrated with large numbers of large, irregularly polygonal cells with moderately vesicular nuclei and a small amount of acidophilic cytoplasm. These cells did not occur as glands or in cord-like formation, but as single cells, having the appearance of epithelial cells. The surrounding blood vessels showed perivascular cuffing with lymphocytes. No histopathology was noted in the remaining brain substance.

Pituitary. On gross examination, the gland appeared small, but not otherwise abnormal.

Histologic examination showed apparently normal chromophobe, acidophilic, and basophilic cells arranged in the usual architecture. There was narrowing of the pars intermedia, and the fibrous septum separating it from the posterior portion was perhaps more prominent than usual. The few remaining cords of the posterior pituitary were relatively well formed and well preserved, and lay in normal relationship to the rest of the gland. The small cord-like structures and semi-cystic spaces were well defined. There were rare groups of nervosa cells which showed definite areas of what appeared to be an early coagulation necrosis. The arterioles about such areas were freely patent. Comparison of the posterior lobe with several others led to the conclusion that this portion of the gland was distinctly hypoplastic.

Thyroid. Weight, 5 gm., distinctly smaller than normal. Histologic examination was negative, except for a slight general increase in connective tissue.

Adrenals. Combined weight, 10 gm. These glands appeared atrophic. On section, the cortex was narrowed to a golden brown band no more than 1 mm. wide. The medulla was represented by a mere gray line.

Microscopic examination revealed no evident histopathology.

Pancreas. Weight, 50 gm. It appeared small and atrophic, but showed no noteworthy changes on histologic examination.

Genitalia. The external genitalia were poorly developed and infantile. The testicles were in the scrotum and were small and firm. No tubules could be strung out from the cut surface. Histologic sections revealed a marked general increase in interstitial tissue with poorly-defined tubules, the cells of which were of prepubertal character and showed a complete lack of spermatogenesis.

The seminal vesicles and prostate were grossly small and infantile. Sections through the prostate revealed chiefly fibro-muscular tissue and small, atrophic, gland-like spaces.

Except for bronchopneumonia, the other organs showed no relevant pathology other than their small size.

The final diagnoses were: Craniopharyngioma, involving the frontal lobes, and the lateral, third and fourth ventricles; hypoplasia and degeneration of the posterior lobe of the pituitary; microsplanchnia; bronchopneumonia.

Case 2, J. O'N., a 70-year-old, white male entered the hospital for the first time on 7/15/40, complaining of extreme weakness since February, 1940.

Past history. Revealed that a gun-shot wound at the age of 14 had resulted in loss of his left eye and part of his hard palate and maxilla on the left. He had malaria at 22. When 61 he developed pleurisy with effusion on the left. He required two thoracenteses, but was told that no evidence of tuberculosis was found.

Present illness. His health had been generally good until January, 1937, when, following unusual exertion, he felt extremely fatigued. Rest was unavailing. He steadily grew weaker, lost appetite and ambition, and by April, 1937, had lost 45 pounds. He was cranky, constipated, and slept poorly. If he stood up quickly, he became very dizzy. Frequently, he felt faint, but never fainted. On April 30, 1937, he was finally admitted to another hospital where he was studied for three weeks.

The hospital report showed that he weighed 159 pounds on admission. Blood pressure dropped in a few days from an initial level of 108/66 to 82/58 mm. Hg. Physical examination was otherwise non-contributory.

Laboratory data showed his urine and blood count to be normal. Wassermann and Kahn reactions were negative. Chemical tests of the blood were normal. Gastric analysis, gastro-intestinal x-rays, and stools were normal. Chest x-rays showed old tuberculosis in the left upper lobe. B.M.R. was minus 33 per cent.

A diagnosis of adrenal insufficiency and hypothyroidism was made. Treatment consisted of adrenal cortical extract 1 cc. every other day, and thyroid 0.06 gram t.i.d. B.M.R. rose to minus 9 per cent by May 12th and shortly afterward was plus 3 per cent. Blood pressure rose to 120/72 mm. Hg at discharge on May 21.

Following discharge, he took 3 cc. of cortical extract daily until late July, when he stopped it because of an apparent diuretic effect. He continued with thyroid 0.12

gram daily until mid-August, when he felt so well that he stopped it. By October he had regained 20 pounds. At this time blood pressure was 138/86 mm. Hg. He was advised to resume thyroid 0.09 grams daily, and he continued this until February, 1940. During this period he felt strong and worked steadily.

In February, 1940, he again overexerted and shortly afterward had a recurrence of his former symptoms of weakness, faintness, and lassitude. An electro-cardiogram at this time showed regular rhythm, low voltage in all leads, normal P-R interval, upright T-waves in all three leads, slight slurring of the QRS complex in *leads 2* and *3* with slight elevation of the S-T segment. He was advised to stop thyroid and to resume cortical extract, 2 cc. daily. Digitalis was administered for a short time, but was stopped as he felt no improvement.

Because he had improved in 1937 after he had gone North for the summer, he decided to leave Florida and return to his former home in Massachusetts. On arriving in Boston he felt so weak that he applied for admission to this hospital. He stated on admission that he had been troubled by a headache, usually frontal, but sometimes generalized, nearly every morning during the past year, and that he had fainted several times during the preceding spring.

Physical examination. Well-developed and fairly well-nourished male showing evidence of weight loss and considerable weakness and unsteadiness on his feet. Skin was smooth and dry with a yellowish pallor. No unusual pigmentation of skin or mucous membranes was present. Hair on head was white and dry. There was very little body hair, chiefly a small amount on the forearms and scanty, white pubic hair. Left eye enucleated with deforming scar of left side of face. Right pupil reacted to both light and accommodation. Vision appeared normal with glasses. Fundus seemed to be normal. Thyroid not felt. Heart was not enlarged. There was a soft apical systolic murmur. Blood pressure was 120/70 mm. Hg on admission. There were a few râles at the left lung base that cleared on deep inspiration; otherwise, the lungs were normal. Abdomen was not remarkable. Genitalia appeared normal for the age. On rectal examination, no definite prostatic mass could be felt. Tendon reflexes were present and normal. There was very slight edema of both ankles. Peripheral arteries were moderately thickened.

Laboratory data. Urine was normal except that the specific gravity was fixed at 1.008 to 1.012. Red blood cell count on admission was 3.33 million with 68 per cent hemoglobin. White blood cell count was 6.1 thousand with 46 per cent polymorphonuclears, 46 per cent lymphocytes, 6 per cent monocytes and 2 per cent basophils. On discharge, red cell count had risen to 4.62 million with 85 per cent hemoglobin. White cell count was 7.7 thousand with 64 per cent polymorphonuclears, 28 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. There was a tendency toward a lymphocytosis during his stay that gradually reverted toward normal. Blood Hinton was negative. Stools were positive for occult blood on all but two occasions, although sigmoidoscopic examination and a gastro-intestinal series and barium enema showed no evidence of a lesion in the gastro-intestinal tract other than a duodenal diverticulum. Spinal fluid was under normal tension and showed no abnormality on microscopic and chemical examination.

Roentgenograms of the skull showed an enlarged sella turcica with slight thinning of the dorsum. The appearance was thought to be suggestive of an intrasellar tumor. The lungs showed a few calcified deposits at the left apex, thought to represent healed minimal tuberculosis.

Clinical course. The patient was afebrile during his stay At first his chief difficulty appeared to be weakness and lethargy for which there was no ready explanation. Blood chemistry and the gastro-intestinal series gave no clue to his disease, and the skull x-rays were considered by the neurological consultant not to be diagnostic. Because of the history of improvement on adrenal cortical extract and thyroid medication, an attempt was made to settle the question of Addison's disease by means of the sodium deprivation test as described by Wilder et al. (5) The results are recorded in figure 3.

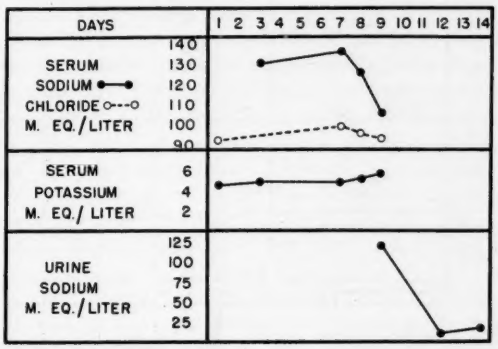

FIG. 3. *Case 2.* CHANGES IN SERUM SODIUM, CHLORIDE, AND POTASSIUM during course of salt deprivation test carried out on *days 7, 8* and *9*. There was a striking fall in urinary sodium following termination of the test.

At first, there was little noticeable change. However, on the second afternoon of the test, he vomited, and repeated this the following day. Appetite remained poor. On the third day after the test, he complained of persistent headache, anorexia, nausea and marked weakness. He was given 5 per cent glucose in normal saline intravenously and 5 mg. of desoxycorticosterone acetate intramuscularly. Shortly afterward he was much improved, but the next day felt very weak and nauseated once more. Glucose and saline intravenously then gave immediate relief. During this period, the blood pressure was not strikingly lowered, although readings of 90/50–60 mm. Hg were made several times.

This reaction, when correlated with the blood Na, K and Cl and the urinary sodium excretion, appeared consistent with a diagnosis of Addison's disease. Accordingly, the patient was placed on a diet moderately low in potassium and was given 6 gm. of NaCl in addition to his diet daily, as well as desoxycorticosterone acetate intramuscularly at approximately weekly intervals.

On this regimen he held his weight, gained in strength and planned to return to work. Following discharge he was seen regularly for 6 weeks during which period he gained weight and showed no more than minimal ankle edema at any time. Then he returned to Florida.

During the fall and winter his strength failed despite weekly injections of desoxycorticosterone acetate and 6 gm. of NaCl daily. He became lethargic and despondent. By March, 1941, his appetite had become very poor, and he began to vomit occasionally. Two weeks before his final admission on 4/8/41 he omitted the NaCl because of anorexia, nausea and vomiting. As he continued to fail he decided to return to this hospital for further study.

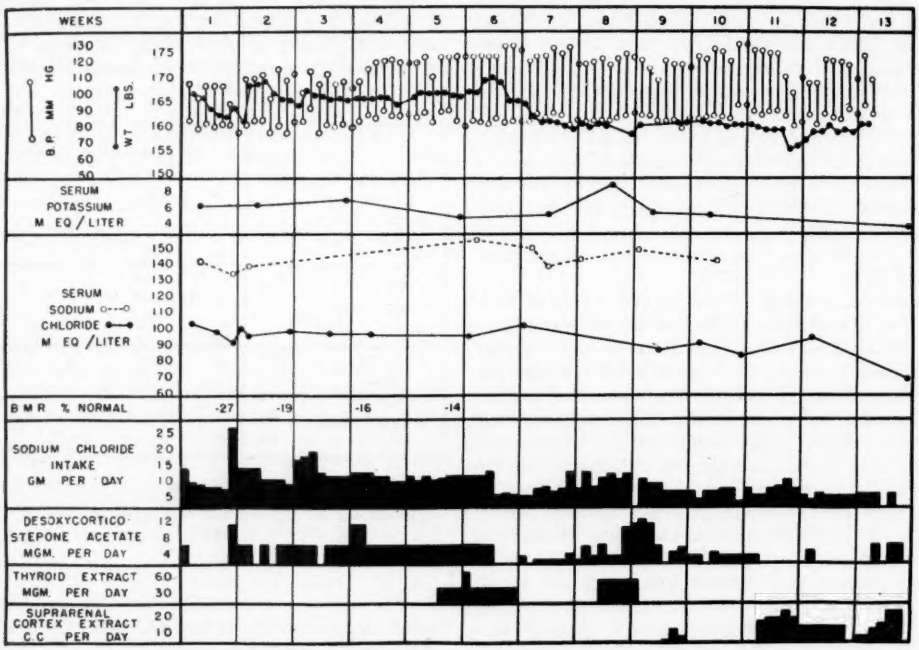

FIG. 4. *Case 2.* SUMMARY OF THE CLINICAL AND LABORATORY RESPONSE TO TREATMENT.

Physical examination on readmission showed no significant change. There was moderate pitting edema of the legs, and the blood pressure was 104/68 mm. Hg. His course until death was quite variable. As is shown in figure 4, his weight tended to fluctuate roughly according to his NaCl and desoxycorticosterone acetate intake. For a time he gradually improved; his blood pressure was fairly well maintained, and he was able to be up and about. However, he had occasional vomiting episodes and was quite frequently bothered by a dull headache. During his second month in the hospital he was given a trial of thyroid extract, because he had felt better, in the past while taking thyroid. After 7 days he developed pleuritic pain on the left and showed signs of fluid, confirmed by x-ray. At this time, he also had peripheral edema and a higher blood pressure than at almost any other time. Reduction of salt and discontinuance of desoxycorticosterone acetate injections and of thyroid led to improvement. When thyroid was readministered, 10 days later, further vomiting resulted, so that it was stopped permanently. Whether there was any change in metabolic rate as a result of this medication cannot be stated, as a determination was not made after thyroid was started.

Eventually it became apparent that desoxycorticosterone acetate and salt were not adequate therapy. A trial was then made of suprarenal cortical extract with apparently good results. After a larger supply was obtained, this was administered as shown in figure 4, in place of desoxycorticosterone acetate. Nevertheless, the patient failed steadily, eventually lapsing into coma and dying.

Necropsy. (Performed 1 hour and 25 minutes after death). *Brain.* Other than a moderate amount of arteriosclerosis, the brain showed no significant pathology.

Pituitary. The sella turcica was enlarged anteroposteriorly and laterally. Both posterior clinoid processes and the base of the sella were eroded and friable. The pituitary gland bulged from the sella, impinging on the posterior aspect of the optic chiasm. The gland was very soft and presented, on sectioning, a bulging, moist pale pinkish-gray surface, upon which no gross nodule could be discerned.

Microscopic study revealed an encapsulated nodule composed of sheets of normal-appearing chromophobe cells subdivided into lobules by a fine, vascular stroma, that comprised most of the gland. About the periphery was a

narrow, incomplete ring of compressed pituitary tissue, consisting of chromophobe, rare eosinophilic, and very rare basophilic cells. The pars intermedia contained a few cystic spaces lined with flattened epithelium and filled with colloid material. The posterior lobe was compressed, but was not otherwise remarkable.

Thyroid. Weight, 15 gm. This was soft and slightly smaller than usual. Sections showed the acini relatively uniform with completely involuted lining epithelium and filled with colloid.

Adrenals. Total weight, 15 gm. They were firm, smooth, and regular in outline, but somewhat reduced in size. No gross abnormality was noted on cut section. Microscopic examination showed the cortex well supplied with lipid and small foci in which the cortical cells were disintegrating and being invaded with lymphocytes, endothelials, and rare neutrophils. The medulla was not remarkable.

Pancreas. Weight, 60 gm. Grossly and microscopically this gland was not remarkable.

Genitalia. There was little of note grossly. Microscopically, the testes showed complete aspermatogenesis. The cells of the tubules were in various stages of disintegration, and the lumen of the tubules was more or less filled with amorphous, acidophilic débris. The interstitial tissue was edematous with slight cellular infiltration.

Heart. Hypertrophy was obvious and there was moderate coronary sclerosis.

Lungs. Bronchopneumonia, fibrocaseous tuberculosis, and healed pleuritis were present bilaterally.

The final diagnoses were: Chromophobe adenoma of the anterior lobe of the pituitary with pressure atrophy of both anterior and posterior lobes; complete involution of the thyroid; atrophy and focal necrosis of the adrenal cortices; senile atrophy of the testes; bronchopneumonia and fibrocaseous tuberculosis; myocardial hypertrophy with moderate coronary sclerosis.

DISCUSSION

It seemed evident during prolonged observation that *Case 1* represented a characteristic example of anorexia nervosa. He presented the emaciation, weakness, and low metabolic rate generally seen in anorexia nervosa, and probably had loss of sexual drive, as he appeared to have ceased to masturbate. Against this view was his lack of the restless drive which seems typical of functional anorexia (3), but his past history suggested that behavior abnormalities were to be expected. The improvement accompanying control of his diabetes insipidus and inception of a supervised regimen was thought to confirm the diagnosis of anorexia nervosa. Finally, the onset of definite visual changes indicated that an expanding intracranial lesion was behind all his symptoms.

The absence of calcification in the craniopharyngioma made early detection impossible. Unfortunately, this tumor belonged among the 20 per cent that, according to Cushing (8), fail to show detectable supra or intrasellar calcification. To judge from the location of the tumor, the disturbed water-balance was the result of encroachment upon the supraopticohypophysial tracts. This would be consistent with the work of Fisher, Ingram, and Ranson (9) which showed that only lesions that destroy the posterior lobe of the hypophysis or the supraoptic nuclei or interrupt the neural pathways between the former and the latter result in diabetes insipidus. This syndrome occurred at some time in 15 per cent of the 101 verified cases of Simmonds' disease reviewed by Escamilla and Lisser (1). Whether the severity of the diabetes insipidus lessened as the anterior pituitary failed is not shown by their data. From the work of Ranson et al. (9), however, this must have been so, as they found that destruction of the anterior pituitary in animals with experimental diabetes insipidus resulted in cure of the latter condition. Likewise, it has long been recognized that total hypophysectomy does not lead to diabetes insipidus, the suggested explanation (9) being that the anterior pituitary exerts a total diuretic influence without which the loss of the anti-diuretic principle of the posterior pituitary can exert no detectable effect upon fluid balance. In this connection it is interesting to note that the diabetes insipidus of *Case 1* appeared to decrease in severity as anterior hypophysial failure became more pronounced.

The failure of pathologic examination of *Case 1* to reveal unquestionable evidence of anterior pituitary damage might be considered to disprove the diagnosis of Simmonds' disease. Escamilla and Lisser (1) reviewed 14 cases that were clinically typical but showed normal pituitaries. Although they did not include them among their proved cases, they suggested that 6 had definite pathology in such close proximity to the anterior lobe that interference with its function was readily conceivable. An attempt was made to prove the diagnosis of Simmonds' disease by the use of the insulin tolerance test and the urinary 17-ketosteroid assay, as advocated by Fraser and Smith (10). The first test showed only a slight fall in blood sugar, only suggestive evidence of hypoglycemia unresponsiveness, and a return to the fasting level at 90 minutes. The second test gave a low value —2.5 mg. per 24 hours—but not the zero value (under 1 mg. per 24 hours) stated (10) to be characteristic of Simmonds' disease.

Despite the facts cited, the clinical course and non-pituitary necropsy findings in this case were so consistent with those shown by unmistakable instances of anterior pituitary failure that little doubt was permissible that this boy's pituitary had ceased to function significantly.

Case 2 offered no such difficulty in diagnosis on the necropsy findings. His anterior pituitary had been massively destroyed by the growth of a chromophobe

adenoma. However, clinically the diagnosis was not clear for a long while, despite x-ray evidence of enlargement of the sella turcica with thinning of the dorsum. These changes were of slight degree and were considered of doubtful significance by the neurological consultant. Also, the patient's response to thyroid and adrenal cortical extract suggested that his adrenal cortices were primarily insufficient. The clinical response to the salt deprivation test seemed to support this view, as did the marked improvement following desoxycorticosterone acetate and salt therapy. Likewise, the appearance of the patient suggested myxedema rather than pituitary cachexia. It gradually became plain, of course, that the cortical insufficiency was secondary and that the positive response to salt deprivation was the type of response that caused Stephens (4) to advocate the test as a method of diagnosing anterior pituitary failure. The myxedematous appearance coincided with the findings of Sheehan (6) and Castleman and Hertz (7) in cases of Simmonds' disease.

SUMMARY

The clinical course and necropsy data in two cases of Simmonds' disease are presented.

One occurred in a boy of 18 who had a craniopharyngioma that resulted in diabetes insipidus and, finally, in signs consistent with anterior pituitary failure.

The other occurred in a man of 70 who suffered from a chromophobe adenoma.

The difficulties encountered in differentiating between anorexia nervosa and Simmonds' disease are stressed, as well as the confusion that may arise because of the predominance of signs and symptoms resulting from hypothyroidism and hypo-adrenocorticism secondary to anterior pituitary failure.

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Acromegalic Gigantism without Cardiac Enlargement:

Report of a Case

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ACROMEGALY is usually associated with skeletal overgrowth and splanchnomegaly. Most observers regard cardiac enlargement as an essential feature of the disease.

The causative factor in the production of enlargement of the heart has been variously ascribed to *a*), direct hormonal activity (1); *b*), degenerative changes in the arterial vascular system (2); *c*), compensatory hypertrophy in response to the ever increasing demands of disproportionately rapid overgrowth of the body (3); and *d*), to alteration in the shape of the cavity of the chest (4).

Cameron (5) stated that the organs enlarge, especially the heart. Cecil (6), Goldzieher (7), MacCallum (8), Sternberg (9), Marie and Souza-Leite (10), and others, believed that the heart participates in the general somatic and visceral enlargement. Englebach (11) stated that 'the heart is enlarged proportionately to the body growth.'

Hinsdale (2) described the changes in the heart as a true sclerotic myocarditis. Pathological studies by Cushing and Davidoff (12) have shown an increase in the amount of muscle fibers and supporting connective tissue, the enlargement being a concentric hypertrophy. In one of their cases the heart weighed 480 gm., but it seemed small in considering the size of the chest. *Case IV* of their series was a 21-year-old woman with advancing acromegaly. The heart weighed 460 gm. In two others of their series, the hearts weighed 1000 and 1050 gm., respectively. Osborne (13) reported a case of acromegaly in which the heart weighed 1275 gm.

The extent to which the heart participates in the morbid changes of acromegaly is recognized by the frequent occurrence, in these cases, of a true cardiac syndrome. There is dyspnea, cyanosis, general weakness, and syncope. As the disease progresses, there is edema and albuminuria. Death usually occurs at an early age from heart failure.

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The following case is of interest because the heart is not involved in spite of a well-established and marked degree of acromegaly.

CASE REPORT

The patient is a 34-year-old male who began to show excessive growth at the age of eight. By the time he was 16 years of age he had attained almost his present height. At an early age he experienced intractable headache, progressive impairment of vision and weakness. Elsewhere he had been given a course of radiation to the pituitary gland which resulted in symptomatic relief. The amount of growth after the age of 16 is not definitely known, but it appears to have been relatively slight.

Physical findings of greatest interest were his physical proportions. He was 228.6 cm. (7 ft., 6½ in.) tall and had a span of 236.2 cm. (92 in.). His weight was 163.3 kg. (359 lb.). His chest circumference was 119.0 cm. (46.4 in.).

Examination of the heart and lungs revealed no significant abnormality. The heart rate was 60 per minute and the blood pressure 149/90 mm. Hg.

Roentgenological examination showed the typical acromegalic changes in the skull (fig. 1). The bones showed enlarged trabeculae. There was expansion of the diploic table and a marked hyperpneumatization of the paranasal sinuses and mastoid cells. The sella turcica measured 11 × 14 mm., its floor being somewhat depressed and irregular. There was a moderate degree of prognathism but very marked progeneum.

The hands measured 25.4 cm. (9.9 in.) in length and showed the usual bony changes of acromegaly (fig. 3).

The thorax was of particular interest. Fluoroscopic examination revealed a cardiac rate of 60, with normal rhythm and amplitude of contractions. There was no abnormality of contour. The lungs were luminous and there was normal respiratory excursion of the diaphragm.

Measurement of the teleroentgenogram (fig. 2) showed the internal transverse diameter of the chest to be 36.0 cm., transverse diameter of the heart 12.0 cm., length 15.0 cm., cardio-thoracic ratio 33 per cent, area 117.7 sq. cm.

Comparison of these cardiac measurements with tables of standard average measurements shows that the heart in this case is not only not enlarged, but much smaller

FIG. 1 (*upper*). SKULL SHOWING TYPICAL CHANGES OF ACROMEGALY. Note coarse texture of bone, expanded diploic table, marked hyperpneumatization of paranasal sinuses and mastoid cells, prognathism and progeneum. The sella turcica is enlarged and irregular. FIG. 2 (*lower*). TELEROENTGENOGRAM OF CHEST. Transverse diameter of lungs 36.0 cm.; transverse diameter of heart 12.0 cm.; cardio-thoracic ratio 33 per cent; length of heart 15.0 cm.; cardiac area 117.7 sq. cm. According to several standards, the heart is 56–66 per cent of the predicted normal value for a man of this size.

than the average normal for the size of the patient. The predicted cardiac area for the patient's height, weight, and age, based on the tables of Hodges and Eyster (14), is 188.07 sq. cm., while according to the tables of Claytor and Merrill (15), his predicted area is 210.6 sq. cm. His actual cardiac area, obtained with a planimeter, was 117.7 sq. cm. This is only 62.1 per cent of the predicted normal area according to Hodges and Eyster's values and 56.0 per cent of Claytor and Merrill's.

According to Danzer's ratio (16), the transverse diameter of the heart in this case could be 18.0 cm. without being considered enlarged. Thus the transverse diameter is only 66.6 per cent of the predicted possible normal value. It is therefore of interest to check the size of the heart in this case according to other standards.

In previous studies, reported elsewhere (17), we have found the transverse diameter of the average normal heart to be 45 per cent of the pulmonary field. In this case of acromegaly the transverse diameter of the heart is 33 per cent of the transverse diameter of the pulmonary field. Accordingly, we find the heart to be only 64.4 per cent of the normal average value for a man this size. On the basis of the unscientific and empirical standard that 'a man's heart is as large as his clenched fist' we find such disparity between the size of the heart and the size of the hand, that, even though the roentgenogram was made with the hand extended, it is again obvious that the heart is small in this patient.

COMMENT

The absence of cardiac enlargement in this case appears to be of more than academic interest. Post-mortem studies by other observers (18) have shown cardiac enlargement to be an almost constant finding in the fatal cases. Moreover, the usual clinical picture includes a long period of cardiac insufficiency and ultimate failure. The patient presented in this report may be considered an arrested acromegalic giant. While his skin is extremely sallow, he presents no cyanosis, dyspnea, palpitation, edema or ascites. For many years associated with a well-known circus as a 'giant' he has, for the past two years, been engaged as sales promotion manager of a large business enterprise —a task equal to the efforts of any healthy and energetic businessman. His avocations are many and

FIG. 3. ROENTGENOGRAM OF HAND in comparison with that of a normal average-sized adult.

varied so that his daily activities may be compared with those of any normal adult.

That the heart was not enlarged in undoubtedly a factor in the better health enjoyed by this patient in comparison with most acromegalic giants. On the basis of tables of normal average measurements, we have reconstructed the patient to fit the size of the heart in this case and find that he should be 179 cm. (5 ft., 9½ in.) tall, weigh 79 kg. (174 lb.), and have an internal diameter of the chest of 26.6 cm. These changes are shown graphically in figure 4.

SUMMARY

An unusual case of an acromegalic giant is presented, in which the heart is not enlarged. Comparison with several different standards shows the heart to be between 56 and 66 per cent of the predicted normal size for a man of his height, weight, and age.

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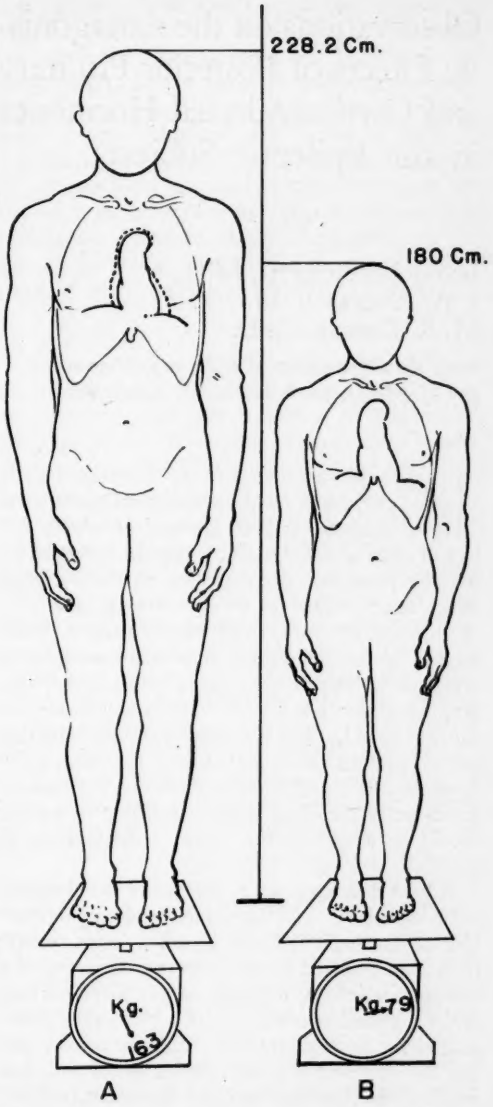

Fig. 4, A. Schematic representation of acromegalic giant and heart drawn to scale. Height, 228.6 cm. (7 ft., 6½ in.); weight, 163.3 kg. (359 lb.); pulmonary field, 36.0 cm.; transverse diameter of heart, 12.0 cm.; length of heart, 15.0 cm. Dotted outline indicates size heart should be according to prediction tables. Transverse diameter of heart, 16.2 cm.; length of heart, 18.6 cm. B. Man drawn in proportion to the size of the heart of the acromegalic giant. Height, 179.0 cm. (5 ft., 9½ in.); weight, 79 kg. (174 lb.); pulmonary field, 26.6 cm.; transverse diameter of heart, 12.0 cm.; length of heart, 15.0 cm.

Observations on the Antagonistic Effects of Posterior Pituitary and Cortico-Adrenal Hormones in the Epileptic Subject[1]

[Epilepsy]

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PROGRESS IN the development of a rational method of therapy for the so-called idiopathic form of epilepsy has been impeded greatly by our lack of exact knowledge concerning the nature of the peculiar physiological disturbance within the brain which is responsible for the spontaneous occurrence of generalized convulsions in afflicted persons. While gross or microscopic lesions undoubtedly occur in the cerebrum in many patients placed in this clinical category, they cannot be found in all, by any means. On the other hand, it has been observed repeatedly that not all persons exhibiting such brain lesions suffer from convulsions. Obviously, therefore, the immediate cause of the characteristic tendency to seizures should be sought in the realm of disturbances in cerebral physiology.

Recent developments in the use of the electroencephalograph (1, 2) for recording the electrical potentials of the brain (i.e., the so-called 'brain waves') have demonstrated beyond any question that the symptom which we recognize as an epileptic seizure is the outward manifestation of a profound disturbance in the electrical rhythm within the cerebral cortex. The different types of seizures (*grand mal, petit mal* and psychomotor variants) show different and highly characteristic brain wave forms. Presumably, the spontaneous development of abnormal electrical potentials on the surfaces of brain cells in certain foci is due to some underlying defect in cell membrane structure and function, or to some other factor interfering with the maintenance of normal relationships between the electrically charged elements within the brain. To determine the nature of such abnormalities and to find adequate means for their prevention or eradication is the primary purpose of scientific investigations in this field. The present preliminary report deals with one aspect of the problem.

Some years ago McQuarrie and Peeler (3) discovered that typical *grand mal* seizures could be induced almost at will in epileptic patients maintained on low-mineral dietaries by increasing their water intake and at the same time administering the antidiuretic, posterior pituitary hormone (pituitrin or pitressin) at regular intervals in doses sufficiently large to prevent water diuresis. Non-epileptic control subjects showed no convulsive reaction to the procedure, although their general physiological response was the same. Since it has been shown that the absolute amount of sodium chloride excreted by the kidneys is increased during periods of pitressin antidiuresis while water is being retained, it is obvious that the extracellular fluids of the body ultimately become diluted by this procedure, providing that the sodium chloride intake of the subject is kept below a certain level. Gilman and Barbour (4) demonstrated this directly by finding increased vapor tension of the blood serum of dogs under similar conditions. That dilution of the extracellular body fluids (or the accompanying disturbance in electrolyte balance brought about by the forced excretion of the Na and Cl ions) constitutes the essential provocative factor is indicated by the demonstration that seizures could not be induced in this manner if NaCl was administered during the period of the test in amounts sufficient to prevent such dilution. This conclusion regarding the rôle of body fluid dilution and associated disturbances in electrolyte relationships in the artificial induction of seizures was further confirmed by the clinical observations of Ziskin and Ziskin (5), who found it unnecessary to administer pitressin to obtain such results, if epileptic patients could be induced to drink water at the rate of 6 to 8 liters daily.

Since it has been demonstrated (6) that cortico-

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adrenal extract and synthetic desoxycorticosterone (7) produce effects on the water and mineral exchanges of the body, which are in many respects diametrically opposite to those of pitressin, it was thought desirable to determine the response of epileptic patients to these cortical hormones. Our objective in the present investigation was not only to ascertain the effectiveness of the adrenal cortical hormone in preventing the seizures, which would otherwise be expected to occur spontaneously, but also to determine how it might alter the patient's convulsive response to the pitressin antidiuresis test. Complete electrolyte and water balance studies, as well as serum electrolyte analyses, were carried out in the case of one severely epileptic adult patient who volunteered to serve as an experimental subject. A less elaborate trial was made, also, in the case of a 12-year-old epileptic boy.

The adult patient, *R.*, aged 26 years, was an especially suitable subject for the investigation because he had an 18-year record of typical *grand mal* seizures, in some of which he had sustained such severe injuries as multiple fractures of the mandible, loss of teeth and lacerations of the tongue. *Petit mal* seizures likewise occurred at times, particularly during the earlier years of his illness. He was a highly intelligent, former college student, which fact made coöperation entirely satisfactory. Repeated neurological examinations, as well as pneumoencephalography and serological tests, made during the previous year by members of the Department of Neuropsychiatry, revealed no evidence of organic disease of the central nervous system. He gave the history of having responded fairly well to the ketogenic dietary regimen at an early age, but within recent years he had found that phenobarbital and mebarol were required in ever-increasing doses to prevent the occurrence of seizures at daily or even shorter intervals. This form of medication produced extreme sluggishness of his mental processes and slurring and excessive slowness in his speech, which made it impossible for him to secure employment. Unfortunately, dilantin in fairly large doses had failed to prevent his *grand mal* attacks, when given a trial several months prior to the beginning of the clinical investigation reported here.

During the week preceding his admission to the hospital for special study, the patient was requested to omit all medication in order that its effects might not influence the experimental results. Upon admission to the University Hospital on April 28, 1941, he was immediately placed on a standard, low mineral diet served in four equal meals at 6-hour intervals. He was maintained on this without modification until the time of his discharge. The total water intake amounted to 2600 cc. daily. During a 4-day preliminary control period on this regimen without medication, he had three severe *grand mal* seizures, indicating that the effects of his previous barbiturate medication had largely worn off. Throughout the succeeding 13 days he was given desoxycorticosterone acetate[2] intramuscularly in doses of 5 mg. every 6 hours. At the end of one week on this treatment, he was subjected to the pitressin test, receiving 0.5 cc. of pitressin subcutaneously every 3 hours night and day while the administration of desoxycorticosterone acetate was continued. A control pitressin test was carried out 4 days after discontinuance of the desoxycorticosterone acetate treatment.

RESULTS

The results of the desoxycorticosterone-pitressin experiment and those of the control pitressin test are presented graphically in figure 1. As indicated on the chart, three spontaneous convulsions (C) were observed during the preliminary period before administration of desoxycorticosterone acetate was begun, whereas none occurred during the next 7 days. This freedom from convulsive attacks was tentatively interpreted as an indication that the desoxycorticosterone acetate exerted a protective influence against spontaneous epileptic seizures. An attempt to test the effect of this synthetic hormone on the occurrence of pitressin-induced seizures was then made.

Near the end of the third day of pitressin administration, a moderately severe *grand mal* seizure occurred, within 2 hours after the patient had dutifully drunk 900 cc. of water in a short period of time to make up the total intake prescribed for the day. Continuation of the desoxycorticosterone acetate for 36 hours after withdrawal of the pitressin greatly accentuated the post-pitressin diuresis and appeared to ameliorate the unpleasant aftermath of the convulsive attack. When the control pitressin test was performed 4 days following discontinuance of the desoxycorticosterone acetate, the patient began to have seizures within 12 hours, before he had had time to store a large amount of extra water. Since none of the three seizures occurred within an hour after administration of the antidiuretic agent, and so appear not to have been due to cerebral vascular effects, the interpretation of an internal shift in the water and electrolytes of the brain was assumed as a factor in the causation of the attacks. Seizures temporarily ceased to occur, as usual, soon after pitressin was withdrawn and the induced disturbances in water and electrolyte balances had disappeared.

Measurements of the daily intake and output of the various electrolytes during the course of the experiment showed distinctly greater retention of sodium and chloride during the period of treatment with

[2] The desoxycorticosterone acetate was supplied by the Schering Corporation, Bloomfield, N. J.

desoxycorticosterone acetate than during the preliminary control period. The potassium excretion, on the other hand, was increased by the desoxycorticosterone acetate during the first 4 days. As indicated by the body weight curve, water was initially retained with Na and Cl as a result of administration of desoxycorticosterone acetate. This response was followed shortly, however, by a diuresis which persisted until pitressin administration was begun. Contrary to expectation, the retention of Na was increased when pitressin was given in addition to desoxycorticosterone acetate. At the same time the excretion of K and that of Cl was increased. Exact data relating to the electrolyte excretion during the day following the seizure are not available because an undetermined amount of urine (one large voiding) was lost. The effect of desoxycorticosterone acetate on K excretion during the period of recovery from the pitressin experiment appears to have been modified by the latter, since it was much less during the 3 post-pitressin days than before. The retention of Cl and Na, as well as the freedom from seizures, for 4 days following omission of desoxycorticosterone acetate suggests a 'carry over' effect of the latter. During the following control pitressin-test period, however, the excretion of Na and of Cl was greatly increased, while K was retained in the body. These effects were, therefore, diametrically opposite those characteristically produced by desoxycorticosterone (7). Except for reduction in serum K, the blood electrolytes were unaltered.

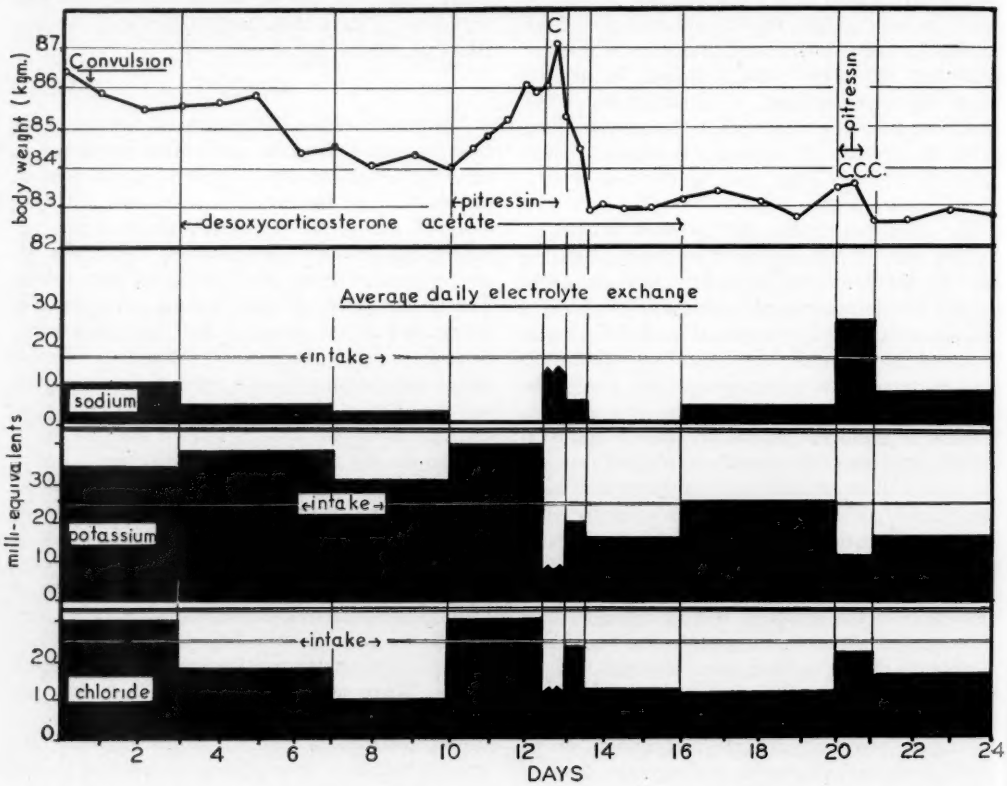

FIG. 1. ANTAGONISTIC EFFECT OF DESOXYCORTICOSTERONE ACETATE on the seizure-provoking action of pitressin in epileptic subject. Low-mineral diet. 2600 cc. of water per diem. Columns in black represent average daily excretion of electrolytes in urine.

Following completion of these short experiments, the patient was discharged from the hospital on an ordinary mixed diet with desoxycorticosterone acetate in sesame oil intramuscularly in doses of 10 mg. daily as the sole therapeutic agent. Because of reported untoward effects of too-long use of this synthetic hormone in large doses (8), the patient was examined at frequent intervals and the serum K was determined weekly.

The apparent result of this therapeutic trial was that he remained free from seizures for 46 days. The first seizure to occur after this comparatively long interval followed reduction of the dosage of desoxy-

corticosterone acetate to 5 mg. daily. This reduction in dosage was considered desirable because the serum K was found to have decreased to 11 mg. per 100 cc. and the blood pressure had become elevated to 150 systolic and 112 mm. Hg diastolic. Within a few days after withdrawal of the desoxycorticosterone acetate, however, these values returned to normal without immediate recurrence of seizures. The patient's mental reaction and his speech became essentially normal with cessation of seizures, so that he was able to hold an office position after leaving the hospital. Whether or not the mental sluggishness and 'thickness' of speech which was present until the desoxycorticosterone acetate was given were due entirely to the previous barbiturate medication, to the effect of seizures, or was associated with the primary brain cell abnormality is problematical. Since withdrawal of the desoxycorticosterone acetate in August, 1941, the patient has remained almost entirely free from seizures by restricting his water intake sufficiently to maintain the specific gravity at or near 1.030. No medication has been given.

A second severely epileptic patient, *E.R.*, aged 12 years, when subjected to similar experiments with desoxycorticosterone acetate, likewise showed a decided prolongation of the time required for induction of a *grand mal* seizure by means of pitressin antidiuresis and forced water drinking. Placed on treatment with desoxycorticosterone acetate in a dose of 5 mg. daily and given an ordinary mixed diet, he remained seizure-free while under our observation for more than 3 months, except for occasional *petit mal* attacks.

DISCUSSION

It is apparent from these preliminary observations that desoxycorticosterone acetate exerts a protective effect against the induction of *grand mal* attacks in the epileptic subject by means of pitressin antidiuresis and forced water drinking. Spontaneously occurring seizures of the *grand mal* type also appear to be lessened in number or prevented entirely by this hormone under certain conditions. *Petit mal* seizures may not be affected to the same extent. The general effects of desoxycorticosterone acetate on the water and electrolyte exchanges of the body are the same in the epileptic as in the normal subject. The specific action of the hormone in causing retention of Na and Cl in the extracellular body fluid, thereby tending to prevent dilution of the latter, appears to be crucial. Increased excretion of water is likewise important, except when excessive amounts of pitressin are given. We are now attempting to determine whether or not changing of the K content of the brain cells and serum plays an important part in reducing the convulsive tendency.

While epileptic patients do not show any of the ordinary signs of adrenal cortical or renal insufficiency their abnormal convulsive response to increased water intake and forced pituitary antidiuresis resembles the increased sensitiveness of adrenalectomized animals to 'water intoxication' in which convulsions occur (9, 10, 11). Desoxycorticosterone (12) and other adrenal cortical steroids (13) have been shown to protect the latter animals against 'water intoxication,' just as desoxycorticosterone in the present investigation was shown to protect our epileptic patients from the convulsive effects of forced dilution of the extracellular body fluids.

Whether or not other cortical hormones would be so effective as desoxycorticosterone acetate in protecting the epileptic subject against spontaneous or pitressin-induced seizures cannot be said until comparative tests have been carried out. It may be mentioned in passing, however, that we observed some protective effect against spontaneously occurring *grand mal* attacks in one severely epileptic patient in 1935, when a whole cortical extract (kindly furnished by Dr. E. C. Kendall) was administered at regular intervals. The finding by Eversole, Gaunt and Kendall (13) that Kendall's compound *E* (17-hydroxy-11-dehydrocorticosterone) was greatly superior to desoxycorticosterone acetate in protecting adrenalectomized rats against the effects of excess water intake suggests that this substance should be given a trial in epileptic subjects when it becomes available in sufficient quantity for that purpose.

The anticonvulsive effect of dehydration frequently observed in epileptic patients subjected to severe water restriction (14, 15), diuresis or catharsis (16) appears to the present authors to be due to its influence on the electrolyte relationships in the various fluid compartments of the central nervous system. By proper adjustments of the dosage of desoxycorticosterone acetate (or other cortico-adrenal steroids) and the intake of water, K, Na and Cl, an improved method of therapy might be developed to effect the same end in a physiological, as well as a much more tolerable, manner. In the present state of our knowledge, however, this form of therapy cannot be recommended for general use. Additional physiological and clinical studies are in progress.

SUMMARY

1. The effects of desoxycorticosterone acetate on the water and electrolyte exchanges and on the occurrence of *grand mal* seizures was determined in two severely epileptic patients.

2. It was found that this synthetic cortical adrenal hormone effectively antagonized not only the electrolyte responses, but also, under the conditions represented in these experiments, the seizure-provoking

effect of the antidiuretic posterior pituitary hormone (pitressin).

3. Preliminary therapeutic tests indicated that desoxycorticosterone decreases the tendency to spontaneous occurrence of *grand mal* seizures, also.

4. The probable mechanism of this action is discussed.

5. The results presented tended to confirm our earlier conclusion regarding the nature of the convulsive mechanism in genuine epilepsy.

6. Possible dangers from prolonged, indiscriminate administration of desoxycorticosterone acetate contra-indicate its use until further investigations now in progress have been completed.

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Addisonian Crisis Complicated by Relative Hypertension, Edema, and Acute Streptococcus Hemolyticus Infection of the Throat

[Addison's Disease]

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THE PROGRESS in the treatment of Addison's disease received considerable impetus with the synthetic preparation of desoxycorticosterone acetate by Steiger and Reichstein (1). Clinical reports began to appear attesting to its efficacy in this disease (2–5) and, indeed, the enthusiasm manifested in these reports was well merited. The patients in Addisonian crisis responded satisfactorily and the distortion in the blood electrolyte pattern so characteristic of the crisis was promptly corrected. However, toxic manifestations, such as hypertension, edema, and heart failure resulting from overdosage with the drug were observed (4, 5).

We have under our observation a patient with Addison's disease who developed acute adrenal insufficiency while under treatment with desoxycorticosterone acetate. The crisis was complicated, and perhaps even precipitated by a hemolytic streptococcic tonsillitis. The picture was unusual in that the adrenal insufficiency occurred while the patient had a relative hypertension and diffuse edema. Treatment with large doses of cortical extract, intravenous fluids, and sulfadiazine resulted in recovery. Recently, Thorn and Lewis (6) reported the successful treatment of two patients with Addison's disease who developed acute hemolytic streptococcic tonsillitis. They commented upon the necessity of supplementary treatment with cortical extract in addition to the use of desoxycorticosterone acetate, sulfadiazine and intravenous fluids.

CASE REPORT

The patient is a 59-year-old white Russian housewife, who had been ill for 8 years preceding the present admission to the hospital. During this period she had frequent episodes of abdominal distress and vomiting. Five years ago her blood pressure was noted to be low. Approximately one year ago she was admitted to the Mount Sinai Hospital for study. At the time of admission she complained of marked weakness, loss of 25 pounds in weight, anorexia, nausea and vomiting, and darkening of the skin. Upon investigation, the blood pressure was found to be 60/40 mm. Hg. She had typical Addisonian pigmentation, and abdominal roentgen-ray studies revealed extensive calcification in the regions of the adrenal glands. The blood sodium at the time of admission was 123.4 m.eq. per liter, the chlorides 94 m.eq. per liter. The urea N was 21 mg. per cent. She was markedly dehydrated. Treatment was started with intravenous isotonic saline, injections of desoxycorticosterone acetate intramuscularly, and the administration of salt by mouth. There followed a prompt remission of the symptoms with a return of the blood sodium and chloride concentration to normal levels, and an increase in the blood pressure to 110/70 mm. Hg. She was then maintained with daily intramuscular injections of 1 to 2.5 mg. of desoxycorticosterone acetate, plus 6 gm. of supplementary salt by mouth. On this regimen she felt well, and the blood pressure, weight and blood sodium concentration were maintained within normal limits.

One week before the present admission to the hospital, the patient noted slight puffiness of the face and edema of the ankles, and her family physician found her blood pressure to be 140/90 mm. Hg. She complained of weakness, anorexia, and some nausea. She omitted one injection of desoxycorticosterone acetate, but the next day resumed injections of 1 mg. of the drug plus the 6 gm. of salt by mouth. During the course of the next 2 or 3 days the ankle edema subsided, although the puffiness of the face persisted. Two days before admission to the hospital the blood pressure was 130/80 mm. Hg, but the asthenia and nausea were more pronounced. The blood sodium was 123 m.eq. per liter and the chlorides 94 m.eq. per liter. It was evident that despite the relative increase in blood pressure and the edema that the patient was developing adrenal insufficiency.

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[1] Charles Klingenstein Fellow.

Upon admission to the hospital the patient appeared acutely ill. She complained of marked weakness and nausea, although no vomiting had ensued. There was moderate edema of the face and eye lids. The blood pressure was 150/90 mm. Hg, the blood sodium was 116 m.eq. per liter, the chlorides 78 m.eq. per liter. The urea N was 10 mg. per cent, while the serum proteins were 6.3 gm. per cent. The hematocrit was 30, the hemoglobin was 77 per cent, and the white blood cell count was 4800 with a normal differential. The examination of the urine was negative. At this time no evidence of pharyngitis or tonsillitis was observed. Four hours after the hospital admission the patient began to vomit and the blood pressure fell to 110/70 mm. Hg. It was now obvious that she was in severe adrenal insufficiency despite the presence of edema, a low hematocrit, and normal or slightly elevated blood pressure. In view of these phenomena it was felt advisable to change from desoxycorticosterone acetate to adrenal cortical extract. Accordingly, she was given 20 cc. of extract[2] intravenously and 10 cc. twice a day subcutaneously. In addition, a constant intravenous infusion of 5 per cent glucose in isotonic saline was given. The following morning there was considerable improvement and the blood pressure varied between 125/84 and 100/70 mm. Hg. The same regimen, however, was continued, and 36 hours after the intensive therapy was instituted she felt quite well. The blood sodium was 126.8 m.eq. per liter and the chlorides 95 m.eq. per liter. It is interesting to note that despite the administration of 2800 cc. of fluids intravenously the edema had subsided.

Two days after the hospital admission her temperature rose suddenly to 103° and the next day to 105.4° F. Examination at this time revealed a markedly injected and edematous pharynx with startling swelling of the tonsils. Hemolytic streptococci in large numbers were cultured from the throat. Concomitant with the febrile reaction there occurred a drop in the blood pressure to 95/60 mm. Hg, and a pronounced fall in the blood sodium to 116 m. eq. per liter. The adrenal cortical extract was increased to 50 cc. a day, of which 30 cc. as well as an initial dose of 4 gm. of sodium sulfadiazine followed by 1 gm. every 4 hours, were administered intravenously. In addition, the constant intravenous infusion of 5 per cent glucose in isotonic saline was continued. During this two-day period, the patient appeared desperately ill. The temperature remained at 105° F., and she was completely disoriented. On the morning of the third day, the temperature fell precipitately to 100° F., and from this point on recovery was fairly rapid. When recovery was well advanced, the intravenous medication and fluids were discontinued and the amount of adrenal cortical extract given subcutaneously was gradually reduced to 4 cc. per day. In addition, she now received 8 gm. of salt orally. The sulfadiazine in doses of 1 gm. every 4 hours was continued for 3 days after the temperature returned to normal levels. Ten days after admission, the patient was perfectly well; the blood sodium and chlorides were 132.9 m.eq. per liter and 102 m.eq. per liter, respectively, and the blood pressure was 120/80 mm. Hg.

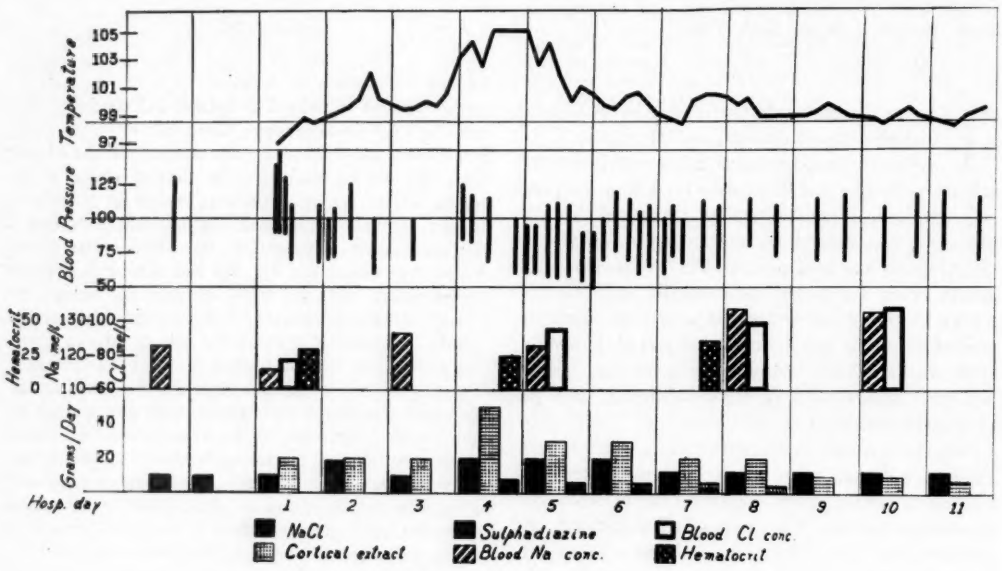

FIG. 1. SUMMARY OF CASE.

DISCUSSION

The asthenia, nausea, vomiting, and low concentration of blood sodium and chloride on hospital ad-

[2] The cortical extract was supplied by The Upjohn Co., Kalamazoo, Mich.

mission were indisputable evidence of a severe Addisonian crisis in a patient with known Addison's disease. The clinical and chemical picture was unusual in that she had neither hypotension, hemoconcentration, azotemia, nor dehydration. This dissociation of the individual manifestations of adrenal insufficiency would further support the concept that more than one hormone is concerned with the regulation of adrenal cortical function. This has its clinical corollary in the recognition that desoxycorticosterone does not by any means represent complete replacement therapy. It has been noted repeatedly (3, 5, 7, 8) that this compound exercises little effect on the disturbance in carbohydrate metabolism in Addison's disease. That other functions of the adrenal cortex may not be possessed by desoxycorticosterone is suggested by the work of Ingle (9) who showed that it did not exert as potent an effect on the muscle work capacity of adrenalectomized rats as some of the other crystalline factors. Finally, Britton and Kline (10) have pointed out that adrenalectomized cats in acute insufficiency respond more promptly and completely to adrenal cortical extract than to desoxycorticosterone acetate. It should be emphasized that desoxycorticosterone is an invaluable drug in the treatment of Addison's disease, but occasionally clinical circumstances arise which necessitate supplementary treatment with, or substitution of, whole adrenal cortical extract.

The development of acute upper respiratory infections has always been a serious complication in patients with Addison's disease. Such infections have usually been difficult to control and have usually been associated with high fever, poor leucocyte response, spreading infection, and the development of signs and symptoms of acute adrenal crisis. With the advent of the newer and less toxic sulfonamide compounds and the intelligent use of the more potent cortical extracts, the lives of many of these patients can be saved.

SUMMARY

A case of Addison's disease is reported in which acute adrenal insufficiency occurred while under treatment with desoxycorticosterone acetate and in the presence of relative hypertension and edema. The problem was further complicated by the development of acute tonsillitis due to hemolytic streptococci. Recovery followed the administration of sulfadiazine, whole adrenal cortical extract, and intravenous fluids and transfusions.

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Prevention of Diabetes Mellitus[1]

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IN THE LITERATURE on the prevention of diabetes one finds attention drawn to the fact that heredity, race, and obesity are among the important factors that influence the development of this disease. If one could choose a mate with no diabetic taint in the family and not develop obesity the incidence of diabetes could be appreciably reduced.

Strome and Blaine (1) point out that mortality rates from diabetes are higher in the United States than in any other major civilized country and that these are increasing every year.

In 1933 the author (2) suggested that if one could diagnose diabetes before it became clinically apparent and could treat the disturbance successfully a considerable step forward in reducing the incidence and mortality of this disease would be achieved.

The author has previously reported (3) that approximately 15 per cent of patients of college age having glycosuria on one examination would have some degree of disturbance of carbohydrate metabolism as judged by routine glucose tolerance tests. The present report deals with results of clinical studies and periodic glucose tolerance tests made on some 90 patients who had various degrees of disturbed glucose tolerance over a period of 9 years.

CLASSIFICATION OF PATIENTS

Patients found to have disturbed glucose tolerance were placed in one of the following groups: *Group I, diminished tolerance.* The blood sugars were normal throughout the tolerance tests[3] except that the initial rise after ingestion of glucose was above 180 mg. per cent. *Group II, diminished assimilation.* Normal fasting blood sugar and no blood sugar above 180 mg. per cent during the test, but a failure of the 2½-hour blood sugar to return to normal (120 mg. per cent or below). *Group III, diminished tolerance and assimilation.* Normal fasting blood sugar (120 mg. per cent or below), and all other blood sugars during the test above normal. *Group IV, diabetes mellitus:* A) Chemical diabetes; all blood sugars above normal e.g., a typical diabetic glucose tolerance test, but no clinical symptoms of the disease. *B)* Chemical findings the same as in previous group and, in addition, one or more clinical symptoms of the disease, such as polyuria, nocturia, increased thirst and fatigue.

PROCEDURE

No patient was included in this study who had evidence of hyperthyroidism, infection, liver disease, or previous diagnosis of a disturbed glucose tolerance. Patients were classified into various groups on a basis of the results of the tolerance tests. During the first two years of the study individuals of comparable age, sex and tolerance were divided within each of the four groups. One half of these were placed on diets; the other half served as controls. Periodically these individuals were given glucose tolerance tests and were observed for signs and symptoms of diabetes. At the end of this time several things became apparent: *a)* Diabetes was not acute in its onset but was a very gradually developing disturbance that became progressively worse if not treated. *b)* The difference in response between the treated and control patients in *Groups I* and *II* was not significant. During the rest of the period of study (1933–40) only those patients whose tolerance tests classified them in *Groups III* and *IV* were consistently followed by periodic observation, tolerance tests, and treatment.

TREATMENT

Therapy consisted of diet alone. The diet was of the restricted fat (approximately 56 gm.), low caloric type. The patient was placed on a diet of carbohydrate, 56, fat, 56, protein, 42, until the fasting blood sugar was below 120 mg. % and postprandial glyco-

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[1] Read before the twenty-fourth annual Meeting of the Association for the Study of Internal Secretions, June, 1940. Delay in publication of this article was deliberate. The method of preventing diabetes described herein was given to several clinics to try for a year in order to see what could be accomplished. So far the results have been gratifying and I believe a method for the prevention of diabetes has been established.

[2] Present address: Battle Creek Sanatarium, Battle Creek, Michigan.

[3] One hundred gm. of glucose in 250 cc. of water was used in all cases.

suria disappeared; then 18 gm. of carbohydrate and 3 gm. of protein (approximately 1 slice of bread or its equivalent) was added (case 8). If postprandial glycosuria appeared, the patient was kept at this dietary level until the urine was sugar-free and again the same amount of carbohydrate and protein was added. The diet was gradually built up to maintenance by this procedure. If glycosuria appeared constantly after any single increase, the diet was reduced to the previous level and maintained there until the glycosuria disappeared. The diet was then increased in amounts of 9 gm. of carbohydrate and 1.5 gm. of protein instead of 18 and 3 gm., respectively.

In all but a few instances weight,[4] health, and activity could be maintained by keeping the fat at a low level as carbohydrate and protein were added. In several instances, however, it was necessary to increase the fat content of the diet 10 or 15 gm. when the carbohydrate tolerance was short of a maintenance diet, and further increase of carbohydrate was not tolerated.

DISCUSSION

The development of clinical diabetes divided itself into several stages *a*, diminished tolerance or diminished assimilation; *b*, diminished tolerance and assimilation; *c*, chemical diabetes; *d*, clinical diabetes (cases 1–4). The onset of clinical diabetes, while it may appear to be acute, is in most instances preceded, for weeks or months, by changes in the blood sugar values which gradually become more severe (case 1).

In this study it was amazing to see how greatly disturbed the glucose tolerance could be and yet not produce clinical symptoms and, conversely, to note that mild disturbances in glucose tolerance in some instances produced clinical symptoms which were quite marked (case 5, 6). The question of why this occurs is as yet unanswered.

The problem of when to begin dietary treatment of a disturbed glucose tolerance is difficult. The findings in this study show that excellent results are obtained when individuals having a diminished tolerance and assimilation, or chemical diabetes are treated Those individuals in the early stages of chemical diabetes respond favorably to diet (case 1, 6, 7, 9). The longer these patients remain untreated and the more symptoms of clinical diabetes that develop, the poorer the prognosis for recovery (case 2, 10).

The author does not believe that treatment should be instigated when an individual is classified in *Groups I* and *II*. Patients of the type in *Groups III* and *IV* should be treated, if the incidence of clinical diabetes is to be reduced. Insulin is not necessary unless clinical diabetes or acidosis are present as, in the author's experience, it has been found to retard recovery in early disturbances in tolerance.

The problem of how long the recovered patient should be kept on a diet is difficult. It seems safe to assume that the diet should be followed for a period of at least one year after recovery and then the patient should be warned to maintain the state of mild undernutrition attained at the time of cessation of the diet. In fully recovered patients, no return of elevated blood sugars or clinical symptoms of diabetes have been noted when this suggestion has been carefully followed.

TABLE 1. RESULTS OF GLUCOSE TOLERANCE TESTS AT THE BEGINNING AND END OF THE DIET PERIOD.

	Fasting	½ hour	1 hour	2 hours	2½ hours
Mean blood sugar when diet began, mg. %	113	188	220	205	179
Mean blood sugar at end of diet period, mg. %	102	152	152	132	107

No explanation as yet can be offered as to why recovery takes place on this regime. Reduction of weight alone was not responsible, as most of the patients were not obese when first seen and they were of practically the same weight at the end of the dietary period as they were at its beginning. That obesity is not an uncommon finding associated with a disturbed glucose tolerance in the older age group is recognized. Twenty-one per cent of these patients with disturbed glucose tolerance had family history of diabetes.

The fact that a normal fasting blood sugar is not a safe index of the severity of the disturbance present is demonstrated (case 7, 11). In considering the significance of an elevated fasting blood sugar in the absence of postprandial glycosuria, the possibility of a high renal threshold for glucose should always be considered (case 2, 3, 6, 8). During this study it was repeatedly demonstrated that the renal threshold may vary in the same individual on different occasions (case 7).

The fact that clinical diabetes can actually be prevented is demonstrated by cases 1, 2, 6, 7, 9, 10, 11 and 12. Cases 3 and 4 are examples of what one sees in those cases which served as controls and were untreated. Table 1 shows the mean bloodsugar values of glucose tolerance tests at the beginning and end of the diet period.

These clinical studies indicate that, by the use of glucose tolerance tests, it is possible to make an early diagnosis of a disturbed carbohydrate metabolism.

[4] Five to 10 per cent under ideal weight as calculated by standard height-weight tables.

CASE PROTOCOLS

Case 1

R. D., male, age 21; referred because of a marked glycosuria. No symptoms of diabetes.

	12/21/32		2/26/34		5/15/34		6/20/34		9/24/34		2/1/35		4/2/35		7/2/35		10/11/35	
	B.S.[1]	U.S.[2]	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.
	No diet		*No diet*		*No diet*		*No diet*		*Diet*[3]		*Off diet*		*Diet*[3]		*No diet*			
Fasting	102	1+	100	0	87	0	120	Tr.	129	0	96	0	118	1+	105	0	109	1+
½ hour	147	4+	182	3+	208	2+	221	4+	240	1+	140	0	179	3+	140	2+	196	3+
1 hour	86	4+	189	4+	217	4+	231	4+	273	4+	167	2+	186	4+	131	4+	120	4+
2 hours	59	4+	107	4+	106	4+	170	4+	176	4+	105	2+	124	4+	68	4+	126	4+
2½ hours	51	4+	55	4+	50	4+	122	4+	138	4+	90	2+	51	4+	53	2+	74	1+
	Wt. 127 lb.				Diminished tolerance		Chemical stage		Wt. 115 lb.; early clinical stage; month preceding, fatigue, polyuria, nocturia		Wt. 122 lb.; recovery; symptoms disappeared		Diminished tolerance		Recovery		Recovery; wt. 126 lb.	

Note: Patient was last seen in 1938. No symptoms of diabetes.
[1] B.S. Blood sugar.
[2] U.S. Qualitative urinary sugar.
[3] Diet: C, 225; E, 56; P, 75.

Case 2

R. B., male, age 19, referred because of glycosuria. No symptoms and negative family history of diabetes. Weight, 98% of normal.

	5/3/38		2/3/39		6/9/39	
	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.
	No diet		Diet[1]			
Fasting	133	0	260	4+	129	0
½ hour	204	0	401	4+	221	0
1 hour	266	4+	455	4+	289	4+
2 hours	241	4+	455	4+	259	4+
2½ hours	212	4+	398	4+	212	4+
	Wt. 145 lb.; early chemical stage; no symptoms		Wt. 142 lb.; clinical stage; polyuria and polydipsia		Wt. 136 lb.; chemical stage; no symptoms	

Note: This patient was seen last in April, 1940. All fasting blood sugars normal and only an occasional trace of sugar after meals.
[1] Diet, C, 164; F, 56; P, 60.

Case 3

A. B., female, age 19; negative family history. Weight, 98% of normal.

	12/23/37		2/24/38		11/27/38	
	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.
	No diet		*No diet*			
Fasting	142	0	147	0	Developed symptoms of diabetes	
½ hour	212	0	226	0		
1 hour	300	3+	273	3+		
2 hours	263	4+	275	4+		
2½ hours	253	4+	248	4+		
	Chemical stage		Chemical stage		Clinical stage	

Note: Patient refused to return in June, 1938, for further study.

Case 4

D. M., male, age 19; no family history of diabetes. No symptoms Referred because of transient glycosuria.

	1/17/36		1/1/37		12/8/37		4/15/40	
	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.
	No diet		*No diet*		*No diet*			
Fasting	75	0	61	0	90	0	130	0
½ hour	106	Tr.	155	2+	162	0	149	3+
1 hour	99		138	3+	152	3+	204	4+
2 hours	91	2+	94	4+	126	2+	170	4+
2½ hours	68	Tr.	98	0	131	1+	147	4+
	Wt. 169 lb.						Wt. 171 lb.; early chemical stage	

Case 5

E. H., female, age 28; no family history of diabetes. No symptoms except mild pruritis vulvae.

	6/3/38		12/20/39	
	No diet			
	B.S.	U.S.	B.S.	U.S.
Fasting	176	4+	157	0
½ hour	259	2+	266	2+
1 hour	315	4+	272	4+
2 hours	337	4+	204	4+
2½ hours	315	3+	170	4+
	Chemical stage		Chemical stage	

Note partial recovery of this patient in spite of no treatment.

CASE 6

R. Dab., male, age 24; referred because of loss of weight, fatigue and transient glycosuria.

	6/2/34		10/25/34		2/25/35		2/4/37	
	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.
	Diet[1]		*No diet*		*No diet*			
Fasting	129	0	72	0	102	0	99	0
½ hour	228	0	72	0	138	0	155	0
1 hour	267	4+	114	0	165	0	196	0
2 hours	186	4+	147	0	98	0	128	0
2½ hours	171	0	110	0	100	0	136	0
	Wt. 144 lb. early clinical stage		Wt. 130lb.; recovered		Wt.145 lb.; recovered		Wt.145 lb.; ? early chemical stage	

[1] Diet, C, 215; F, 60; P, 72.

CASE 7

M. H., male, age 38; referred because of persistent glycosuria. No symptoms.

	5/9/32		12/2/32		5/16/33		11/21/33		6/21/34	
	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.
	Diet[1]		*Off diet*		*Diet*[1]		*Off diet*			
Fasting	74	0	82	0	80	0	96	0	124	0
½ hour	96	0	112	0	135	0	109	0	195	0
1 hour	204	4+	140	1+	165	0	145	Tr.	193	2+
2 hours	173	4+	129	0	167	0	135	1+	217	Tr.
2½ hours	157	3+	105	0	135	0	98	Tr.	163	0
	Wt. 214 lb.; no symptoms; chemical stage?		Wt. 206 lb.; no symptoms		No symptoms		Recovery		Wt. 204 lb.; polyuria, early clinical stage	

[1] Diet, C, 275; F, 56; P, 78.

CASE 8

W. S., age 50; no family history of diabetes. No symptoms except fatigue.

	12/20/39			Date	Diet C	Diet F	Diet P	B.S.	U.S.	Weight, lb.
	B.S.	U.S.								
Fasting	204	0	Patient given dietary therapy. No postprandial glycosuria after 1/15/40. Diet increased slowly as indicated in columns at right.	12/20/39	56	56	42	204	0	178
½ hour	297	2+		1/15/40	74	56	45	124	0	173
1 hour	367	3+		2/ 7/40	92	56	48	124	0	164
2 hours	350	3+		4/ 2/40	182	60	63	116	0	162
2½ hours	310	4+								
	Wt. 178 lb.									

CASE 9

M. T., male, age 54; negative family history of diabetes and no symptoms.

	4/23/36		2/24/37		8/5/38	
	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.
	Diet[1]		*No diet*			
Fasting	217	2+	99	0	49	0
½ hour	295	4+	140	1+	107	0
1 hour	327	4+	173	0	109	0
2 hours	315	4+	131	Tr.	114	0
2½ hours	277	4+	69	Tr.	81	0
	Chemical stage; wt. 185 lb.		Recovered; wt. 150 lb.		Recovered; wt. 173 lb.	

Note: Patient last seen in 1939. Had no symptoms or postprandial glycosuria.

[1] Diet, C, 236; F, 56; P, 72.

CASE 10

E. von B., female, age 50; normal weight. Family history of diabetes. Referred because of failing vision, fatigue, polyuria, polydipsia, and neuritis.

	8/22/39		4/8/40		12/31/40	
	B.S.	U.S.	B.S.	U.S.	B.S.	U.S
	Diet[1]					
Fasting	275	2+	124	0	78	0
½ hour	362	4+	196	0	97	0
1 hour	447	4+	253	0	150	0
2 hours	465	4+	247	2+	172	1+
2½ hours	440	4+	226	2+	153	1+
	Clinical stage		Chemical stage; no symptoms		No symptoms	

Note: This case is presented to show results of treating a severe diabetic early in the development of the disease.

[1] Diet, C, 150; F, 70; P, 55.

If these patients are properly treated by diet alone it is possible to reverse the metabolic process that is taking place and attain a normal carbohydrate metabolism as indicated by the glucose tolerance test. The fact that this can be accomplished indicates that, in diabetes mellitus, the underlying pathology is not necessarily a lack of insulin, but that there may be a failure of its proper utilization by the body.

The answer as to what will ultimately happen to these treated patients can be known only in future years. An attempt is being made to follow all of these patients in order to determine whether or not they develop clinical diabetes in spite of following instructions in regard to the diet and the maintenance of proper weight.

CASE 11

M. F., female, age 62. Negative family history of diabetes. October, 1940, noted symptoms of nocturia, polyuria, polyphagia and gain of 15 pounds of which she had lost 17 pounds by the time she was seen, giving her a normal weight.

	3/14/41		4/22/41	
	B.S.	U.S.	B.S.	U.S.
Fasting	122	0	92	0
½ hour	213	0	166	0
1 hour	278	2+	187	0
2 hours	333	3+	148	0
3 hours	244	2+	80	0

Date	Diet C	F	P	Weight, lb.	Fasting Blood Sugar
3/12/41	56	56	42	140	140
3/23/41	74	56	45	138	120
3/30/41	92	56	48	137½	110
4/ 7/41	110	56	51	134	130
4/17/41	128	60	60	133½	105
8/12/41	150	70	70	126	80

Note: A case of rather dramatic and maintained recovery from clinical diabetes.

SUMMARY

Glycosuria is of clinical significance. The development of diabetes in young adults is slow and resolves itself into four stages, respectively: *a*), diminished tolerance; *b*), diminished tolerance and assimilation; *c*), chemical diabetes; *d*), clinical diabetes.

Excellent results may be accomplished by diet alone, and there may be a return to normal tolerance if therapy is instituted in patients of *Groups III* and *IV, A*. In early clinical diabetes results are satisfactory, but if the condition progresses and severe symptoms occur, good results become more difficult to attain.

In this age group the presence of obesity or a family history of diabetes was not significant in enabling one to predict which of two individuals with disturbed glucose tolerance would ultimately develop diabetes.

Loss of weight alone is not responsible for improvement in tolerance.

The renal threshold for glucose is not stationary.

It would appear that after recovery the individual must continue to restrict his diet and maintain a normal or subnormal weight to be able to retain a normal carbohydrate metabolism.

Diabetes may not be wholly due to a lack of insulin but rather to a failure in utilization of insulin by the body.

REFERENCES

1. STROME, F. B., and B. C. BLAINE: *Pennsylvania M. J.* 43: 481. 1940.
2. WATSON, B. A.: *Minnesota Med.* 16: 566. 1933.
3. WATSON, B. A.: *Endocrinology* 25: 845. 1939.

CASE 12

H. C., male, age 19. Family history of diabetes, weakness, polyuria, polyphagia, polydipsia, and glycosuria 4 months preceding first glucose tolerance test.

	10/9/31		5/6/32		1/1/33	
	B.S.	U.S.	B.S.	U.S.	B.S.	U.S.
	Diet[1]		*Off diet*			
Fasting	113		122	0	238	4+
½ hour	217		176	2+	315	4+
1 hour			231	4+	415	4+
2 hours	388		208	4+	455	4+
2½ hours	340		136	4+	425	4+
	Wt. 150 lb.; clinical diabetes		Wt. 142 lb.; chemical diabetes		Wt. 144 lb.; clinical diabetes	

Note: This patient's second glucose tolerance curve indicates almost complete recovery in that the fasting and two and one-half-hour blood sugars nearly approximate each other.

[1] Diet, C, 275; F, 56; P, 78.

COMMUNICATIONS TO THE EDITORS

Influence of Testerone Propionate on the Size of Uterine Fibroids in Human Male

In a previous communication[1] we were able to demonstrate that small pellets of estradiol benzoate implanted locally into the uterus of guinea pigs produce fibromyomatous tumors in 75 per cent of the animals used. It appeared that androgen implanted simultaneously has a tendency to limit the extent to which the estrogen is able to produce these tumors. In order to determine whether androgen had comparable depressing effects on fibromyonatous tumors in the human female we decided to treat patients having fibroids with testosterone propionate.

This effect has been reported by various workers in the treatment of metrorrhagia in patients in whom fibroid tumors were found to be present. Opinion varies as to the efficacy of this mode of treatment and there are few observations concerning changes in the size of these tumors.

In view of the fact that we will not be able to continue this work further, I would like to report 3 cases in whom testosterone propionate was employed and in whom we were particularly concerned with changes in the size of the uterine fibroids.

Each patient was examined by the writer before, during and after treatment, and by at least one other observer.

Patient 1, Mrs. E. M., a 50-year-old white woman. This patient had a firm uterus the size of a 4-month pregnancy with a subserous tumor on the left side the size of a lemon. This mass on the left side was extremely tender to palpation. She was given 10 mg. of testosterone propionate 3 times a week for 20 injections, followed by 3 injections of 25 mg. The menses, which had been regular, continued to be regular although the menstrual flow was somewhat diminished. After 4 injections the pain in the left lower quadrant disappeared; after 17 she was examined and the uterus was found to be smaller, the nodule on the left being about the size of a walnut and much less tender. One month after treatment had been stopped, pelvic examination revealed the uterus as slightly larger than normal with only a suggestion of a tumor on the left side. Four months later, 5 months after treatment had been stopped, both the uterus and the fibroid on the left side were found to be larger although not as large as when treatment was originally begun.

Patient 2. Mrs. I. P., a 44-year-old white woman whose chief complaint was profuse menstrual flow, was found to have fibroids the size of a 3-month pregnancy. She was given 25 mg. of testosterone propionate twice a week for 31 injections. The menses, which had been regular, remained regular with the exception of one month when she did not have a menstrual period; this was early in the course of treatment. The flow became quite normal. At the end of this course of treatment the uterus was found to be slightly larger than normal with a fibroid prominence on the anterior surface. At this time the patient complained of some deepening and hoarseness of the voice, and mild facial acne. One month later the acne had improved and the hoarseness had disappeared. Two months later, 3 months after cessation of treatment, the uterus had regained its original size which has been maintained to date. The menstrual periods have been normal and regular 8 months after cessation of treatment.

Patient 3, Miss N. B., a 29-year-old white woman. This patient was found to have several fibroid masses so that the uterus was the size of a 4-month pregnancy with one large fibroid mass on the left side the size of an orange and extending to the umbilicus. She was given testosterone propionate therapy consisting of 20 injections of 25 mg. each, twice weekly. At the end of this period of treatment the uterus had become smaller, about the size of a 2- to 3-months pregnancy, and the tumor on the left side, was no larger than a lemon. The menses had been irregular, previously, and were similarly irregular during treatment. The patient complained of some deepening of the voice and increase in facial hirsutes.

Discussion. It appears that testosterone propionate may cause a regression in the size of uterine fibroids as well as relieve many of the symptoms produced by these tumors. This effect, however, seems to be temporary, since regrowth occurred in 2 of these patients in whom there was sufficient time to observe the phenomenon.

It would seem that the use of this method of treatment would be limited. Nevertheless, it might prove to be of some value in cases in which it is desirable that the menstrual flow be maintained and in instances in which surgery or x-ray are contra-indicated.

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[1] Perloff, W. H., and R. Kurzrok: Production of uterine tumors in the guinea pig by local implantation of estrogen pellets *Proc. Soc. Exper. Biol. & Med.* 46: 262. 1941

Abstracts of

CURRENT CLINICAL LITERATURE

Editor: DANIEL A. McGINTY. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, BORIS B. RUBENSTEIN, EMMERICH VON HAAM.

THYROID

GODTFREDSEN, E.

Scotopic vision and liver function under thyrotoxicosis. *Acta med. Scandinav.* 108: 261. 1941.

The author investigated the complex interrelations between thyroid function, liver function, serum cholesterol, and vitamin A metabolism. In 10 cases of thyrotoxicosis he found no significant injury to liver nor marked reduction of serum cholesterol. There was however definite reduction in dark adaptation which was not amenable to administration of vitamin A, but which responded to reduction of the thyrotoxicosis, suggesting that there may be a downward regulation of the vitamin A utilization in the organism due to thyreotoxic injury.—*F. R. Vanzant (courtesy Biol. Abstracts).*

JOHNSTON, J. A.

Factors influencing retention of nitrogen and calcium in period of growth. V. Further evidence of the anabolic effect of thyroid on calcium metabolism. *Am. J. Dis. Child.* 62: 1172. 1941.

Continuous determinations of Ca and N balance with concurrent determinations of B.M.R. for the entire time were carried out on 2 girls, who were given desiccated thyroid substance. With a constant intake of food, prolonged bed rest, small doses of thyroid resulted in increased retention of Ca and larger doses produced a decreased retention. The amount of thyroid resulting in a maximal utilization of Ca reduced N retention. Total retention of both was increased by an increased intake of food, which was refused when the metabolism was low and taken well when the metabolism was elevated by thyroid.—*M.B.G.*

KEARNS, J. E., JR., AND P. STARR.

So-called "iodine resistant" hyperthyroidism. *Surg. Gynec. & Obst.* 74: 256. 1942.

A satisfactory method is described for the care of hyperthyroid patients in whom the initial effect of I was not sufficient to insure safe operation and in whom the consequent delay resulted in a rising basal rate with aggravation of symptoms. In these people gradual reduction in the amounts of I given to the point of an I-free diet was practiced. This I-free regime was persisted in for 2 to 4 months with careful observation. Thereafter the patients could be satisfactorily prepared for surgery in the usual way.—*A.T.K.*

KOWALLIS, G. F., S. F. HAINES AND J. DE J. PEMBERTON.

Goiter with associated myasthenia gravis. Report of 3 cases of exophthalmic goiter and 1 case of adenomatous goiter with hyperthyroidism. *Arch. Int. Med.* 69: 41. 1942.

Exophthalmic goiter with associated myasthenia is common, but exophthalmic goiter accompanied by myasthenic gravis of the bulbar type is rare. Three cases of exophthalmic goiter combined with myasthenia gravis of the bulbar type and 1 case of adenomatous goiter with hyperthyroidism and myasthenia gravis are presented in this excellent contribution. In 1 of these cases subtotal thyroidectomy has been performed successfully, with relief of symptoms of both conditions. Surgical treatment of exophthalmic goiter complicated by myasthenia gravis offers certain difficulties. It is important that the patient be able to cough and to swallow in order to dispose of tracheal mucus, which often appears after thyroidectomy. In the instance herein recorded in which thyroidectomy was performed, treatment with prostigmine resulted in satisfactory improvement in muscular strength.—*I.B.*